Hyalinization of the Islets of Langerhans in Diabetes Mellitus

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In 1901 Opie[1] described severe hyalinization of the islets of Langerhans in two cases of diabetes mellitus. He regarded the lesion as evidence that diabetes is due to disease of the islets, but gave no data as to its frequency in diabetes. Warren,[2] in a study of 484 diabetic pancreases, found hyalinization of the islets in 41 per cent. The incidence of hyalinization was 45 per cent in those over 40 years of age, but only 6 per cent in those under that age.

My observations on 1194 diabetic pancreases are in close agreement with those of Warren. The cases are arranged in Table 1 with respect to the age at death and the degree of hyalinization. One or more microscopic sections of the pancreas were studied and the number of islets examined ranged from ten to fifty. It is easily possible that a higher percentage of positive results would have been obtained if several hundred islets had been examined; but it is unlikely that this is a large error since it was noted repeatedly that when the first twenty islets were negative all additional islets examined were likewise negative.

Grade 0 in the table indicates a complete absence of hyaline, and grade 1— indicates a small deposit in an occasional islet. The other numerals are rough indications of the degree and extent of the lesion. A grade 1 lesion is shown in Figure 1. In grade 4 lesions practically all of the islets show massive hyaline deposits (Figure 2). In the lesions graded 1 and 2 there are only small masses of hyaline and a majority of the islets are unaffected. Even in the grade 4 lesions thin cords of islet cells are always seen between the hyaline masses (Figure 2). There is never a complete destruction of islet tissue. Some degree of islet cell insufficiency may have been associated with the grade 4 lesions which were present in 54 cases—about 5 per cent of the entire group—but in 95 per cent of the cases it is clear that hyalinization of the islets was not the cause of the deficiency of insulin.

AGE

In Table 1 it appears that there is a progressive increase in the frequency and intensity of hyalinization with

TABLE 1. Relation of age to hyalinization of the islets.

Age at Death	Total Number	Degree of hyalinization					Per Cent Plus
		0	1—	1	2	3	4	
0-20	23	23	0	0	0	0	0	0.0
20-40	104	95	3	3	3	0	0	8.6
40-50	94	71	4	9	2	7	1	24.4
50-91	973	528	47	152	74	119	53	45.7
	1194	717	54	164	79	126	54	40.0

advancing age. No hyaline islets were found under the age of 20 years, and less than 10 per cent of subjects between the ages of 20 and 40 years showed hyaline changes. About one-fourth of those between the ages of 40 and 50 years, and 45.7 per cent of those over 60 years of age showed some hyalinization. There was no significant increase in the percentage with hyalinization after the age of 50 years. Clearly there is a striking relation between hyalinization of the islets and the age of the individual, yet over one-half of elderly diabetic subjects show no hyaline islets.

SEX

In Table 2 the cases are tabulated with respect to sex and the degree of hyalinization. It appears clearly that the lesion has an equal distribution in males and females.

TABLE 2. Relation of sex to hyalinization of the islets

	Total Number	Degree of hyalinization 0	1—	1	2	3	4	Per Cent Plus
Males	553	333	24	75	33	60	28	40
Females	641	384	29	89	47	66	26	40

DURATION OF THE DIABETES

In Table 3 the relation of hyaline islets to the duration of the diabetes is shown. In 1149 cases in which the approximate duration of the disease was known it appears that there is no significant difference in the incidence of the lesion in those with a duration of less than 10 years and those of over 10 years' duration. In this respect hyalinization of the islets differs sharply from vascular disease which increases in frequency and intensity with the duration of the diabetes.

TABLE 3. Relation of hyaline islets to the duration of diabetes

Age at Death	Duration of Diabetes 0-10 Years: Total Number	0-10 Years: Per Cent Plus	Over 10 Years: Total Number	Over 10 Years: Per cent Plus
0-40	91	6.6	31	9.7
40-91	779	43.4	248	45.1
	870	39.5	279	41.2

THE CLINICAL SEVERITY OF THE DIABETES

Obviously hyalinization of the islets is unrelated to the severity of the diabetes in younger subjects since diabetes in younger persons is seldom mild and hyaline islets are rarely found. The subjects over 50 years of age were divided into two groups: those with mild diabetes controllable without insulin or with small amounts of insulin, and those with moderate or severe diabetes who required moderate to large amounts of insulin. The incidence of hyaline islets was about the same in the two groups.

Of the 54 subjects with severe hyalinization of the islets (grade 4) 23 had mild diabetes and 31 had moderate or severe diabetes. It appears therefore that hyalinization of the islets is not related to the clinical severity of the diabetes.

TABLE 4. Relation of vascular disease to hyalinization of the islets

Age at Death	Patients with Hyalinization: Vascular Deaths No.	Vascular Deaths %—	Nonvascular Deaths No.	Nonvascular Deaths %—
0-40	24	8.3	80	8.7
40-60	137	36.5	173	31.8
60-91	417	53.0	339	41.6

RELATION TO VASCULAR DISEASE

In Table 4 the incidence of hyaline islets is compared in those who died of vascular disease and those who died of other causes. In subjects over 60 years of age there is a small but significant preponderance of hyaline islets in the vascular group.

HYALINE ISLETS IN NONDIABETICS

The opinion is frequently expressed that the demonstration of hyaline islets does not establish the diagnosis of diabetes since hyaline islets are sometimes found in nondiabetics. In 1904 Ohlmacher[3] found severe hyalinization of the islets in a man 72 years of age who had no sugar in his urine during his terminal illness. Saltykow,[4] in 1909, found four cases with hyaline islets in 21 diseased pancreases of nondiabetics. Cecil,[5] in 1914, reported six instances of hyaline islets in nondiabetics. Diabetes was apparently excluded by the absence of glycosuria, no blood sugar determinations being reported.

Wright,[6] in 1927, described five cases with hyaline islets in nondiabetics over 50 years of age. However, in two of his cases there was a trace of sugar in the urine. No blood sugars were recorded. Warren,[2] 1938, mentioned four nondiabetics with hyaline islets. Ahronheim,[7] 1943, found hyaline islets in five of 50 nondiabetics over 50 years of age; and Arey,[8] 1943, reported hyaline islets in 19 of 114 nondiabetics over 50 years of age.

In 200 consecutive autopsies on subjects over 50 years of age with no clinical history of diabetes and no

FIGURE 1 Islet of Langerhans showing moderate hyalinization (grade 1). Photomicrograph

FIGURE 2 Islet of Langerhans showing severe hyalinization (grade 4). Note the few persisting beta cells. Such cells commonly show a few beta granules. Photomicrograph

glycosuria during the terminal illness, I found 5 with hyaline islets. In none of the 5 cases was there a determination of the blood sugar or a glucose tolerance test.

We may conclude from the foregoing observations that hyaline islets are occasionally found in subjects over 50 years of age who had no clinical signs of diabetes and no glycosuria during the terminal illness. But in no instance has mild diabetes been excluded by an appropriate study of the patient prior to the terminal illness. It is well known that mild diabetes in elderly persons is often asymptomatic and that glycosuria and hyperglycemia may disappear in the terminal stages of any disease in which the patient consumes very little food. Mild diabetes in elderly persons may often be well controlled by restricting the carbohydrate intake.

Two cases have come under my observation in which there were no evidences of diabetes during the terminal illness, but hyaline islets were found in the pancreas. However, it was learned subsequently that mild diabetes had been recognized in both of these persons over one year previously. In the absence of the earlier study these cases might have been regarded as examples of hyaline islets in nondiabetics. Mild diabetes has not yet been convincingly excluded in "nondiabetic" subjects that show hyaline islets at necropsy.

THE NATURE OF THE HYALINE DEPOSIT

The hyaline material accumulates in the islets between the cells and the capillary walls in much the same way that amyloid forms in the liver and adrenals. On the basis of staining reactions several investigators have maintained that the hyaline material is amyloid (Ahronheim, Arey). Opie obtained no positive reaction for amyloid; but Warren reported that 14 of 51 cases tested gave a positive amyloid stain. However, a positive reaction with gentian-violet or methyl-violet is not sufficient evidence of the chemical identity of islet hyaline and amyloid.

DISCUSSION

Hyaline islets are closely related to the age of the diabetic subject but not to any other feature of the disease. They are not influenced by the duration or intensity of the diabetes or by the sex of the individual. In 95 per cent of the cases the amount of insular tissue destroyed by the hyaline deposit appears to be insufficient to account for the islet insufficiency. Over 40 per cent of the cases with severe hyalinization were clinical examples of mild diabetes. It may therefore be said that the insufficiency of insulin in diabetes is not due to hyalinization of the islets. Hyaline islets are a

little more frequent in elderly diabetics who die of vascular disease than in those who die of other causes, but there is no other suggestion in this study that atherosclerosis plays a part in the etiology. They are to be interpreted as an associated phenomenon of diabetes rather than as a cause or an affect of the disease. Since they are present in only 40 percent of diabetics they cannot be considered an essential part of the pathological picture. The writer is inclined to believe that hyaline islets are pathognomonic of diabetes although they give no information as to the clinical severity of the disease. It has not been convincingly established that they occur in nondiabetics. We do not know whether they precede or follow the clinical manifestations of diabetes.

SUMMARY

In 1194 diabetic pancreases the incidence of hyaline islets in the several age groups was as follows: 0 to 20 years, 0 per cent; 20 to 40 years, 8.6 per cent; 40 to 50 years, 24.4 per cent; and 50 to 91 years, 45.7 per cent. Hyaline islets were present in 40 per cent of the entire group.

The degree of hyalinization varies from a very small deposit in an occasional islet to almost complete replacement of all the islets; but extreme hyalinization was found in only 5 per cent of the entire group. Hyalinization is not the cause of islet insufficiency.

Hyalinization is related only to the age of the diabetic subject. It is not correlated with the duration or the clinical intensity of the diabetes. It has an equal sex distribution.

It has not been convincingly established that hyalinization occurs in nondiabetics.

Hyalinization appears to be an associated phenomenon of diabetes rather than a cause or an affect of the disease.

ACKNOWLEDGEMENT

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Some Further Studies On the Relationship Of Adrenal Cortical Hormones To Experimental Diabetes

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Many phases of organic metabolism are affected by either adrenal cortical insufficiency or excess. The diabetic animal or patient is especially sensitive to abnormal changes in the function of the adrenal cortex. Diabetes is ameliorated by adrenal cortical insufficiency and is exacerbated by the administration of an excess of cortisone, hydrocortisone or corticosterone. Diabetes is also exacerbated when hypercorticalism is produced by the administration of an excess of corticotropin. It is possible to administer these hormones in dosage sufficient to cause a temporary glycosuria in either normal laboratory animals or human subjects.

It has been imagined that these effects of adrenal cortical insufficiency and excess have made clear the normal role of the adrenal cortex in regulating carbohydrate metabolism. This is not true. Conclusions about the normal role of this quietly functioning organ in body economy represent inferences from observations made under the unusual conditions of experiment or disease. Our inability to make direct observations upon the basic mechanisms of hormone action should make us cautious and humble.

There is no doubt that carbohydrate metabolism is affected by adrenal cortical insufficiency and excess and there is no doubt that the normality of carbohydrate utilization is dependent upon the normality of adrenal cortical function. It is less certain that the adrenal cortex is a prepotent regulator of carbohydrate metabolism.

During the past twelve years I have been concerned with the following question: "What are the metabolic consequences of adrenal cortical activation during various forms of stress?" When the secretory activity of the adrenal cortices is stimulated by large doses of exogenous corticotropin signs of hypercorticalism ensue. During any type of stress the increased release of hypophyseal corticotropin stimulates the adrenal cortex to secrete more of its hormones. Does stress cause a state of hypercorticalism? If so, a stress should cause exacerbation of experimental diabetes due to activation of the adrenal cortices. This paper reviews the results of four experi-

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ments which have a bearing upon this question but which do not yet permit a satisfactory answer.

METHODS

Infection-free male rats of the Sprague-Dawley strain were partially depancreatized at a weight of approximately 275 gm. by the procedure described by Ingle and Griffith.[1] The experiments were conducted in an air-conditioned laboratory with the temperature maintained at 74° to 78° F. and the humidity at approximately 50 per cent of saturation. After the animals had recovered from the operation and had reached a weight of approximately 300 gm. they were placed in metabolism cages and were adapted to the forced feeding of a medium carbohydrate diet (Table I) by stomach tube each morning and late afternoon. The technique and diet were modified from those described by Reinecke, Ball and Samuels.[2] During the period of adaptation to forced feeding the amount of diet was increased gradually to prevent the development of food shock. The animals were brought to a full feeding of 26 cc. of diet per day on the 6th day. Twenty-four hour samples of urine were collected at the same hour each day (8:00 to 8:30 a.m.) and were preserved with toluene. Urine glucose was determined by the method of Shaffer and Williams.[3]

TABLE I—MEDIUM CARBOHYDRATE DIET

	grams
Cellu flour (Chicago Dietetic Supply House)	60
Osborne-Mendel salt mixture	40
Dried yeast (Pabst)	100
Wheat germ oil	10
Cod liver oil	10
Mazola oil + 100 mg. vit. K	10
Mazola oil	190
Casein (Labco)	160
Starch	200
Dextrin	190
Sucrose	200
Water to total of	2000

EXPERIMENTS AND RESULTS

Experiment 1 was a repetition of an earlier study[4] on the relationship of the diabetogenic effect of diethylstilbestrol to the adrenal cortex in the rat. This compound and other synthetic and natural estrogens are diabetogenic in the forced-fed rat. Since certain of the adrenal cortical hormones are diabetogenic and since large doses of estrogen are among the noxious stimuli which cause the adrenal cortices to enlarge, it seemed reasonable to postulate that the diabetogenic effect of this and other estrogens is due to its stimulation of the anterior pituitary-adrenal cortex axis to produce a state of hypercorticalism. However, the following experiment shows that diethylstilbestrol exerts a diabetogenic effect which is not mediated by the adrenal cortex.

Six partially depancreatized rats which were free from spontaneous glycosuria were used in these experiments. Each rat was given 0.1 mg. of diethylstilbestrol by subcutaneous injection once daily for 7 days. All of the rats developed glycosuria during the administration of the estrogen but became free from glycosuria when the injection of estrogen was stopped. At this time all of the rats were adrenalectomized and were treated with 3 cc. daily of beef adrenal extract (Upjohn) for 21 days. The animals remained free from glycosuria during the control period but developed marked glycosuria during the 7 day period that the estrogen was injected. When the administration of diethylstilbestrol was stopped the glycosuria disappeared.

The data of this experiment are shown in Figure 1. It is clear that diethylstilbestrol exerts an effect upon carbohydrate metabolism in the rat which is not mediated by the adrenal cortex, although, as shown in the earlier study[4] the presence of the adrenal cortical hormones is necessary for the full manifestation of the diabetogenic activity of the estrogen.

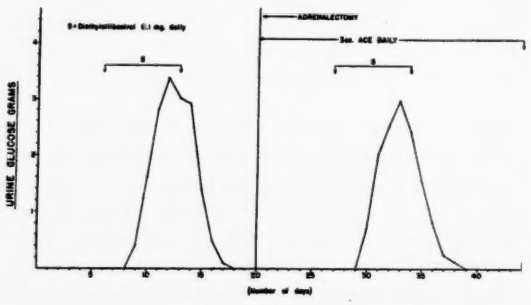

FIGURE 1 The effect of diethylstilbestrol upon the urinary glucose of 6 partially depancreatized rats before and after removal of the adrenal glands. Averages

Experiment 2 was a partial test of the hypothesis that the pharmacologic effects of aspirin are mediated by the release of increased amounts of corticotropin and hence of the adrenal cortical hormones. Hailman[5] has summarized the evidence that aspirin can cause a state of hypercorticalism via stimulation of the anterior pituitary-adrenal cortex axis. If aspirin does cause hypercorticalism it should exacerbate the diabetes of the partially depancreatized rat. The converse happens;[6] the diabetic state is ameliorated. We have compared partially depancreatized rats with adrenalectomized-partially

depancreatized rats in respect to the response to large doses of aspirin. The amount of adrenal cortical extract required to restore the glycosuria to its preadrenalectomy level (3 to 5 cc. per day) was established for each adrenalectomized rat and was then kept uniform throughout the remainder of the experiment. All of the rats showed amelioration of the diabetes during the administration of aspirin with marked exacerbation of the diabetes when aspirin was withdrawn. It was clear that this effect of aspirin can occur independently of any change in the secretory activity of the adrenal cortices. The data are shown in Figure 2.

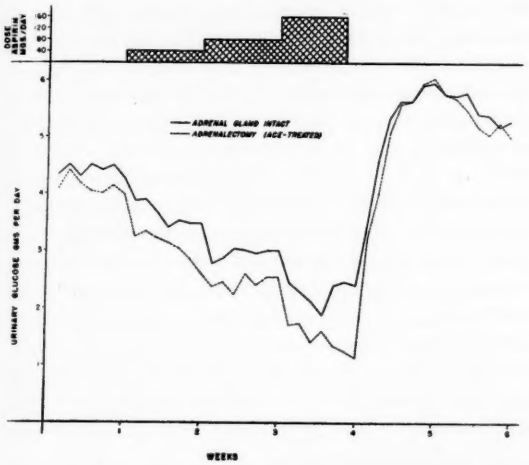

FIGURE 2 The effect of aspirin upon the glycosuria of 6 pairs of partially depancreatized and partially depancreatized-adrenalectomized rats. Averages

Experiment 3 was intended to test the hypothesis that any nonspecific stress should cause exacerbation of the diabetic state in the partially depancreatized rat via the activation of the adrenal cortices by endogenous corticotropin. Adrenalectomized and nonadrenalectomized diabetic rats were compared in respect to the effect of a stress (injections of dilute solutions of formaldehyde) upon the level of glycosuria. These data have been published.[7] Fifteen mildly diabetic rats were adrenalectomized and treated with adrenal cortical extract in amounts which sustained the preadrenalectomy level of glycosuria. An equal number of nonadrenalectomized rats were studied in parallel. The subcutaneous injection of 1.5 per cent formaldehyde, in doses of 0.25, 0.5, and 1.0 cc. twice daily for 7 days, 5 rats per dose level, caused some decrease in the glycosuria of the nonadrenalectomized rats and a much more striking decrease in the glycosuria of the adrenalectomized rats. When the injections were stopped, the glycosuria was reestablished at its preinjection level. The data are shown in Figure 3.

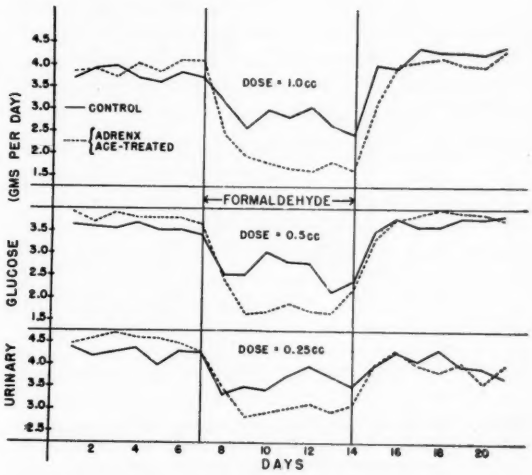

FIGURE 3 Effects of injections of 1.5 per cent formaldehyde on the glycosuria of partially depancreatized and partially depancreatized-adrenalectomized rats. Averages for 5 pairs of rats in each of 3 groups

It has been shown by unpublished experiments in this laboratory that the administration of ethylenediamine causes an increase in the excretion of glucose by the partially depancreatized rat. The adrenal cortices enlarge during the injection of ethylenediamine and it is assumed that there is an accompanying increase in the secretion of adrenal cortical hormones.

Experiment 4 demonstrated that the presence of the adrenal glands is required for the exacerbation of the diabetic state by ethylenediamine. Twelve mildly diabetic rats were used in the study. Six of the rats were adrenalectomized and treated with adrenal cortical extract in amounts which sustained the preadrenalectomy level of glycosuria. An equal number of nonadrenalectomized rats with a similar level of glycosuria were studied in parallel. Ethylenediamine was administered by subcutaneous injection in amounts of 0.05 cc. daily for 5 days and 0.1 cc. daily for 5 days. There was a striking increase in the glycosuria of the nonadrenalectomized rats but there was no increase in the glycosuria of the adrenalectomized animals. When the administration of ethylenediamine was stopped, the glycosuria of the nonadrenalectomized rats fell to the preinjection level whereas the glycosuria of the adrenalectomized rats fell below the preinjection level. The average values for urinary glucose are shown in Figure 4.

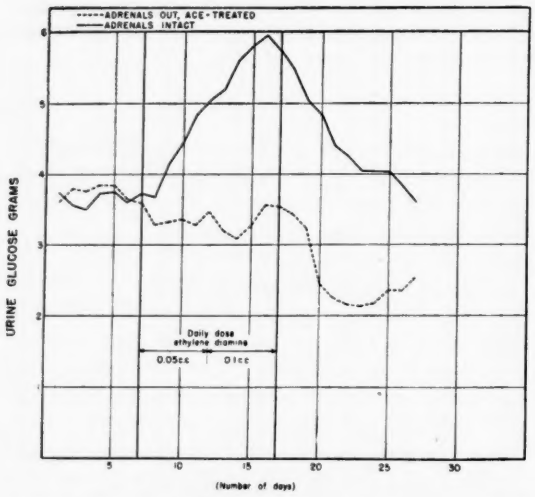

FIGURE 4 Effects of ethylenediamine upon the glycosuria of 6 pairs of partially depancreatized and partially depancreatized-adrenalectomized rats. Averages

COMMENT

In experiments 1 and 2 it was shown that diethylstilbestrol and aspirin have effects upon carbohydrate metabolism which are not mediated by a change in the secretory activity of the adrenal cortices. Although large doses of either of these drugs can cause an increase in the secretory activity of the adrenal cortices there is no satisfactory evidence that the metabolic consequences of this response represent a state of hypercorticalism.

In experiment 3 the injection of toxic doses of formaldehyde was used as a stress to cause activation of the adrenal cortices. It is probable that the increased secretion of adrenal cortical hormones during this stress did have a positive effect upon the level of urinary glucose in that it tended to prevent the marked decrease in glycosuria which occurred in rats without adrenal glands. These adrenalectomized rats which were on a fixed intake of adrenal cortical extract—an amount which represented adequate replacement therapy during non-stress conditions—developed a state of relative adrenal cortical insufficiency during stress and the glycosuria fell sharply as is characteristic of adrenal cortical insufficiency. The consequence of the adrenal response to the stress was to maintain the status quo as far as the level of glycosuria was concerned and not to exacerbate the diabetes and cause other signs of hypercorticalism.

During the past twelve years we have tested for the possible effect of a number of toxic compounds and stressful situations upon the glycosuria of the mildly diabetic forced-fed rat. Among them are phenol, carbon tetrachloride, methadone hydrochloride, lobeline sulfate, dihydrocodeinene bitartrate, nikethamide, furacin, quinine, quinidine sulfate, tartronic acid, cadmium chloride, copper sulfate, sodium arsenate, aluminum chloride, caffeine, benzyl benzoate, betaphenyl-ethylamine, pyrogens, water intoxication and low temperature. Each form of noxious stimulus was gradually increased in severity until the animal died, yet in no case was there any significant rise in the level of glycosuria.

From the results of experiments 1, 2 and 3 and from the negative results obtained by testing the several noxious agents listed above we have drawn the tentative conclusion that the increased secretory activity of the adrenal cortices during stress tends to maintain homeostasis rather than to disturb it. The increased secretion of adrenal cortical hormones serves to meet an increased need for these hormones and does not cause a state of hypercorticalism such as develops when the titer of these hormones is increased artificially in the absence of a need. The results of experiment 4 represent a challenge to this generalization. The exacerbation of glycosuria by ethylenediamine is dependent upon the presence of the adrenal glands and presumably upon the response of the adrenal cortices to this form of stress. The response does not appear in similar animals which have been adrenalectomized and are maintained on a fixed intake of adrenal cortical extract.

Does the injection of ethylenediamine cause exacerbation of glycosuria in the partially depancreatized rat solely because it causes a state of hypercorticalism? This is a possible explanation but it is not the only interpretation that can be made of the data. An alternative hypothesis is that ethylenediamine has some diabetogenic activity of its own but by virtue of also being toxic and stressful the diabetogenic activity is masked by the concomitant production of a state of adrenal cortical insufficiency in the adrenalectomized rats whose intake of exogenous hormone is fixed. Similar animals having intact adrenal glands secrete more hormone during the stress and maintain a state of eucorticalism (not hypercorticalism) thereby permitting the manifestation of the diabetogenic action of ethylenediamine. Thus the response of the adrenal cortex may possibly serve as a supporting cause of the metabolic response without becoming the exciting cause.

The following considerations give some support to the above hypothesis: 1. The fact that the several other forms of stress studied by us have failed to cause exacerbation of diabetes indicates that ethylenediamine

has some effect not possessed by nonspecific damaging agents. 2. It is known that diabetes is ameliorated by adrenal cortical insufficiency. In experiment 3, the relative state of adrenal cortical insufficiency caused by the injection of toxic doses of formaldehyde did cause a decrease in the glycosuria of the adrenalectomized rats which were on a fixed intake of adrenal cortical extract. A similar response could have been expected during the injection of ethylenediamine to the adrenalectomized rats of experiment 4 but it did not occur, possibly because ethylenediamine had some extra-adrenal effect upon the glycosuria. 3. Following the withdrawal of ethylenediamine the glycosuria did fall below its initial level in the adrenalectomized rats which indicates that the compound may have had a positive effect upon glycosuria during its administration. Animals so injected have a considerable amount of necrosis of the skin and therefore remain under stress after the injection of ethylenediamine is stopped.

At the present time we have not excluded the possibility that ethylenediamine affects glycosuria via the adrenal medulla rather than the adrenal cortex.

This paper is a progress report and our interpretations of the data are listed as hypotheses, not conclusions. We expect to continue our studies on the metabolic consequences of adrenal cortex activation during stress.

SUMMARY

These studies were intended to test the hypothesis that nonspecific noxious stimuli can cause exacerbation of a diabetic state via activation of the anterior pituitary-adrenal cortex axis. Partially depancreatized male rats were forced fed a fluid medium carbohydrate diet by stomach tube. In experiment 1, the injection of diethylstilbestrol caused exacerbation of the glycosuria in 6 nonadrenalectomized rats and induced a similar response in the same animals after they were adrenalectomized and kept on a fixed intake of adrenal cortical extract. In experiments 2, 3 and 4 half of the animals were adrenalectomized and treated with amounts of adrenal cortical extract which sustained the preadrenalectomy level of glycosuria during the control periods. In experiment 2 the injection of large doses of aspirin caused amelioration of the glycosuria in both nonadrenalectomized and adrenalectomized rats. In experiment 3 the injection of dilute solutions of formaldehyde caused a small decrease in the glycosuria of the nonadrenalectomized rats and a marked decrease in the glycosuria of the adrenalectomized rats. The results of these three experiments fail to support the hypothesis under test. In experiment 4 the injection of toxic amounts of ethylenediamine caused exacerbation of the diabetes in the presence of the adrenal glands but not in their absence. These results suggest that this stress caused a state of hypercorticalism.

A second possible explanation is that ethylenediamine has a specific extra-adrenal diabetogenic action which is masked by the development of adrenal cortical insufficiency in those adrenalectomized rats whose intake of exogenous hormones was adequate to meet the needs of non-stressful conditions only.

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DISCUSSION

DR. GEORGE W. THORN *(Boston):* In a field as complicated as that dealing with the relationship between the adrenal cortical hormones and insulin secretion, all of us appreciate the beautifully controlled experiments which Dr. Ingle has been able to carry out over a period of several years. It is unfortunate that in our studies of the mechanism of diabetes in man we cannot establish the same rigid control.

There is one point in Dr. Ingle's presentation which I am certain he would like emphasized. Throughout his discussion it has been tacitly assumed that changes in urinary glucose content automatically reflect overall changes in the diabetic state of his animals. With the particular substances which he employed, many of which are known toxic agents, changes in renal threshold may easily occur. Such changes could lead to more or less glucose being present in the urine without necessarily reflecting aggravation or amelioration of the underlying diabetic state.

I should also like to discuss an aspect of Dr. Ingle's work which interests me particularly. This might be

termed a comparison between the flexibility of the intact human to deal successfully with wide changes in carbohydrate metabolism, in contrast to the rigidity or inflexibility of the patient without adrenals or with limited capacity to secrete insulin. My reason for discussing this point at this time is the striking experience many of us have had in administering large doses of ACTH or gluconeogenic adrenal steroids without observing the development of diabetes. On the other hand, occasional patients may develop frank or latent diabetes under such a program. It appears at present that the load imposed by a course of ACTH or cortisone may be one of the most effective means of detecting latent diabetes mellitus and I hope that over the next few years this hypothesis will be tested in a large enough population to establish its validity. Certainly if I were faced today with the necessity of determining the capacity of a patient to produce insulin, I would use first the serum phosphorus response to intravenously administered glucose and follow this by a course of ACTH or cortisone with a subsequent glucose tolerance test carried out before the course of adrenal hormone administration had been discontinued. When glucose tolerance tests are carried out in patients receiving ACTH or cortisone, one must not misinterpret the elevation of the glucose tolerance curve which reflects increased deposition of glycogen in the liver. Under these circumstances, the elevated glucose curve should be accompanied by a normal fall in serum inorganic phosphorus in contrast to the true diabetic state in which this does not occur without insulin. Refined tests of this type are only necessary when the usual glucose tolerance test is negative or when there is a strong family history of diabetes mellitus.

In contrast, the patient with diabetes mellitus and Addison's disease may have his diabetes mellitus markedly aggravated by a daily dose of 25 mg. of cortisone or may become severely hypoglycemic with 5 units of insulin when not receiving a maintenance dose of cortisone. These experiments in man, of course, merely confirm the animal experiments of Long and Lukens in pancreatectomized-adrenalectomized animals.

In our laboratory, Dr. Dalton Jenkins has accumulated evidence that the glucogenic corticoids do not appear to act directly or specifically in antagonizing the action of insulin. In other words, the metabolic changes induced by a given dose of insulin may occur despite the administration of very large quantities of cortisone. These observations, while needing confirmation, do support the thesis which Dr. Ingle has presented, namely: that the role of the adrenal hormones in the genesis of diabetes mellitus is not as specific as formerly considered, but occupies more the position of providing a tissue factor essential for the development of diabetes.

Finally, I should like to say that in our own experiments in man we have not been able to confirm the idea that the additional glucose accumulated with glucogenic steroids arises predominantly from protein sources. Certainly the degree of negative nitrogen balance or increase in total nitrogen excretion is often so small as to make this hypothesis untenable unless associated with some as yet unknown rearrangement in nitrogen metabolism. Certainly the evidence is suggestive that a large factor is the transition to fat utilization with perhaps gluconeogenesis being increased from fat sources.

DR. JEROME W. CONN *(Ann Arbor, Michigan):* I think that someone should emphasize the point that in diabetic humans the stress of major surgery usually increases the severity of the diabetes, at least in the immediate postoperative period.

Although we do recognize evidence of increased adrenal-cortical activity under conditions of stress, the total response to stressful circumstances involves other endocrine activities which have not yet been clearly delineated. It is likely, for example, that there occurs increased activity of the R. Q. depressing factor recently described by Recant.

The point I wish to make is that the human diabetic, exposed to a very stressful situation, does not diminish his glycosuria. Dr. Ingle's well controlled experiments in rats probably do not include all of the factors which are involved when the diabetic patient responds to an "alarming stimulus."

DR. DWIGHT J. INGLE (Closing): The changes in glycosuria that I described to you are accompanied by a marked hyperglycemia, which shows we were not dealing with changes in the renal threshold.

The diabetogenic activity of the adrenal steroids and of corticotropin in experimental animals is similar to the effects of these hormones upon carbohydrate metabolism in man as described by Dr. Thorn. It requires enormous amounts — much larger in proportion than is being used for therapeutic purposes — to cause glycosuria in normal animals. It can be done but it requires 5 or 10 mg. of cortisone per rat per day, for example. Even though a severe insulin-resistant type of diabetes is induced, it does not persist but fades out in time.

We have never been able to sustain steroid diabetes in normal rats, even during the time that we continued to give the hormone, and, of course, it disappears whenever the hormone is withdrawn.

Diabetes Mellitus and Cushing's Syndrome:

*CONCENTRATIONS OF LACTATE AND PYRUVATE IN BLOOD AFTER INGESTION OF GLUCOSE**

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The response of the blood levels of lactic and pyruvic acid to the ingestion of glucose, in the standard glucose tolerance test, has been reported as a reliable criterion of early thiamine deficiency.[1] Also, abnormalities of the blood levels of these two metabolites have been obserevd in diabetes mellitus.[2-4] In a recent publication[5] the hypothesis was presented that determination of blood lactate and pyruvate as well as blood glucose might provide a means of distinguishing between pancreatic diabetes and the hyperglycemias of other than pancreatic origin. In the first part of the present study this subject is given further attention; in the second part some data are provided on the so-called diabetes which at times accompanies Cushing's syndrome.[6]

LACTATE AND PYRUVATE IN DIABETES MELLITUS

A number of investigators[7-11] have previously noted that the concentrations of lactate and pyruvate tended to be elevated in the presence of thiamine deficiency. Horwitt and associates,[12] studying the relationships between the concentrations of glucose, lactate and pyruvate in the blood of normal fasting subjects, found that the

*Abridgement of thesis submitted by Dr. Hills to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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concentrations per 100 ml. approximated 100 mg. for glucose, 10 mg. for lactate, and 1 mg. for pyruvate. They noted further that this 100:10:1 ratio persisted with relatively little variation throughout the course of a standard glucose tolerance test. The levels of lactate lagged a little behind those for glucose; the pyruvate lagged still more; nevertheless, the relationship 100:10:1 remained unmistakable.

In 1927 Katayama and Killian[2] observed less lactate in the blood of diabetics after glucose had been given than in the blood of normal subjects given glucose, and in 1942 Bueding and co-workers,[3] in a selected group of moderately severe diabetics from whom insulin had been withheld for 24 to 48 hours, found either no rise in concentration of pyruvate after glucose was ingested or else a rise that was considerably delayed as compared with the normal. Klein[4] and Himwich and Himwich[13] came to similar conclusions, as did Horwitt and co-workers,[5] who observed that the severe diabetic patient without insulin does exhibit a rise in concentration of blood lactate and pyruvate after glucose is ingested, but only after some delay. There is virtually no increase at the one-hour point, and the maximal elevation is reached only during the second or third hours after the glucose has been given. Thus the ratio between glucose, lactate and pyruvate is distorted, the value for blood sugar being relatively high and those for lactate and pyruvate relatively low. With mild exercise added to the metabolic stress established by ingesting glucose, the diabetic organism responds with a sharp rise of the concentration of lactate and pyruvate.[5, 13] This, on an absolute basis, resembles that seen in thiamine deficiency, but, when considered in the light of the associated very high levels of glucose, does not appear out of proportion. Insulin accelerates the rise of the concentration of lactate and pyruvate which followed giving glucose to the resting diabetic patient. It does not, however, alter the response to exercise.

THE GLUCOSE TOLERANCE TEST Moyer and Womack[14] recently concluded that the one-dose standard glucose tolerance test was the most sensitive and most helpful of the several tests employed for the diagnosis of diabetes. For the purposes of our paper a normal result in a patient receiving 1 gm. of glucose per kilogram of body weight consists of a fasting blood sugar concentration not exceeding 120 mg. per 100 ml., a one-hour level not exceeding 180 mg. per 100 ml., a two-hour level not exceeding 120 mg. per 100 ml., and a three-hour level that is the same as, or below, the fasting level.

The diagnosis of diabetes mellitus can usually be made on the above criteria, provided the patient does not have a concurrent infection or some metabolic disorder such as hyperthyroidism, cirrhosis of the liver, or Cushing's syndrome; also provided the patient has not been fasting or on a diet restricted in carbohydrate.

However, even in the absence of complicating factors, the clinician is faced not infrequently with a difficult diagnostic problem in subjects whose one-hour blood sugar level slightly exceeds 180 mg. per 100 ml. or whose two-hour level remains somewhat higher than 120 mg. per 100 ml. The treatment of diabetes mellitus involves serious modifications of the patient's life, which one is loath to impose unless the diagnosis is conclusively established. Therefore, it was hoped that examination of the concentrations of blood lactate and pyruvate concurrently with that of glucose would add to the reliability of diagnosis based on the glucose tolerance test.

GLUCOSE TOLERANCE TESTS WITH CONCOMITANT DETERMINATIONS OF LACTATE AND PYRUVATE The 46 patients chosen as the subjects of this study had been scheduled routinely for glucose tolerance tests. In some of them a diagnosis of mild or questionable diabetes had been made previously; others were patients who were suspected of having impaired gastrointestinal absorption. All were following an unrestricted and adequate diet and fasted for at least 12 hours before the test. A few were receiving insulin, but if so its use was discontinued 24 hours before the test. None was receiving protamine zinc insulin.

The patients walked to the clinic on the morning of the test and were allowed to rest in a chair for 30 minutes before administration of glucose. When about half the tests had been completed, however, it was noted that the basal levels of lactate and pyruvate in blood were consistently somewhat higher than we expected them to be. This was attributed to the exercise of walking, incomplete relaxation in the chair and nervousness at the prospect of examination. In the remainder of the tests, therefore, the patients were allowed to rest in bed in a private room for an hour before administration of glucose.

The one-dose standard glucose tolerance test employed entailed the withdrawal of blood samples before and one, two and three hours after administering orally 1 gm. of glucose per kilogram of body weight. The glucose was dissolved in 200 ml. of water flavored with lemon extract.

CHEMICAL METHODS The blood was drawn with a minimum of stasis and precipitated in 10 per cent solution of ice-cold trichloracetic acid as recommended by Friedemann and Haugen.[15] It was first transferred from the syringe to a test tube and then precipitated in the trichloracetic acid from a chemically clean Mohr pipet delivering 5 ml. It is recognized that this procedure involves somewhat more elapsed time than the syringe technic recommended by the aforementioned authors. For this reason the average pyruvate values consistently are slightly lower than would be expected otherwise.

Glucose was determined by the method of Folin and Wu.[16] Lactate was determined by the method of Barker and Summerson,[17] as modified by Horwitt and co-workers,[12] and the method for pyruvate was essentially that of Friedemann and Haugen.[15] All samples were analyzed in duplicate, and at least two points on a standard curve were measured with each set of determinations.

OBSERVATIONS When all testing was completed the cases were placed, on the basis of the glucose tolerance curves, in three categories: diabetic, nondiabetic, and borderline diabetic. Then, but not before, the clinical records were examined. It was immediately apparent that the present nondiabetic group of patients could not be considered as "normal." Six of the 12 had impaired gastrointestinal function, and the "flat" curves obtained with their tests might be attributable to poor absorption of the glucose. Likewise, in the frankly diabetic group, only one patient regularly required insulin, whereas, in the group of patients studied by Horwitt and co-workers,[5] all required large doses of insulin.

Table 1 presents the data for the three groups. Of particular interest is the one arbitrarily labelled as "borderline diabetic," consisting of 19 cases. Examination of the tolerance tests in this borderline group of cases reveals the presence of two distinct types of curves with some overlapping. The first type is characterized by hyperglycemia (values of 190 to 250 mg. per 100 ml.) one hour after the ingestion of glucose, and the second by a normal or slightly elevated response after 60 minutes but a markedly delayed recession at two hours. These two categories are presented separately in Table 1 and are labelled "spike" curve and "plateau" curve respectively.

The behavior of the concentrations of pyruvate and lactate in these tests shows (1) that the basal levels of lactate and pyruvate averaged about the same in all groups in spite of numerous individual variations and (2) that the values for lactate and pyruvate increased on the average from 8.0 and 0.8 mg. to 12.0 and 1.0 mg. per 100 ml., respectively, 60 minutes after the ingestion of glucose. These figures emphasize once more the fundamental manner in which the concentrations of lactate and pyruvate differ from those of other blood constituents; namely, that the absolute figures in themselves, as observed in the blood of fasting and resting patients or in the course of a glucose tolerance test, assume importance only when correlated with the corresponding levels of glucose. Finally, the data fail to reveal any obvious manner by which either the borderline group, as a group, or the individual cases therein can be classified as diabetic or nondiabetic. At most there is a tendency for the levels of lactate and pyruvate to be somewhat more indicative of diabetes in the "plateau" than in the "spike" curve group.

Figure 1 shows the average values for the three groups and, for contrast, represents the values for both the severe diabetic and the nondiabetic subjects reported by Horwitt, Hills and Kreisler.[5]

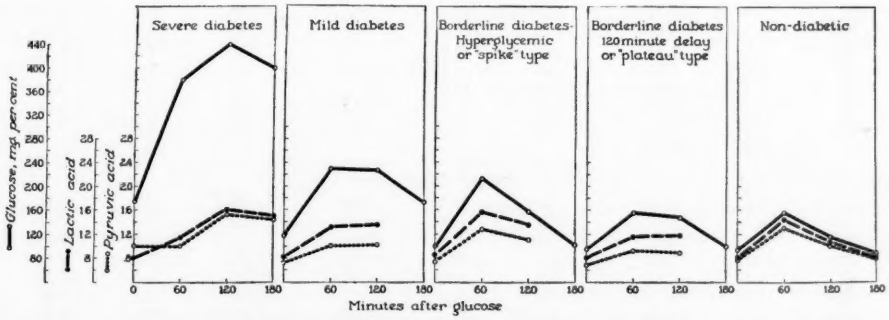

FIGURE 1. **Average values for glucose, lactate and pyruvate in the blood after ingestion of glucose in five groups of cases.**

TABLE I Concentration of Blood Lactate and Pyruvate Determined During Standard Glucose Tolerance Tests
(Values expressed in mg. per 100 ml. of blood)

Case	Basal level			After administration of glucose: 60 minutes			120 minutes			180 minutes
	Glu.	Lac.	Pyr.	Glu.	Lac.	Pyr.	Glu.	Lac.	Pyr.	
Mild diabetic curve										
1*	130	13.4	1.11	220	15.8	1.29	260	16.9	1.61	293
2†	100	7.0	0.90	223	11.8	1.16	235	13.6	1.28	115
3†	115	8.6	0.84	245	11.6	0.83	226	12.4	0.96	153
4†	107	6.7	0.53	217	10.9	0.77	217	11.7	0.94	176
5†	125	6.8	0.40	252	9.5	0.71	267	13.1	1.13	170
6†	144	7.4	0.70	235	12.6	1.18	226	14.2	1.25	213
7†	88	8 3	0.86	235	7.4	0.84	245	9.9	0.85	340
8*	105	6.9	0.71	248	10.9	1.00	327	9.0	0.70	281
9*	208	12.9	1.05	274	15.6	1.06	420	19.6	1.26	323
10*	163	6.8	0.68	274	9.8	0.97	153	9.2	0.85	123
11*	120	12.8	1.16	252	14.4	1.13	208	13 9	0.93	133
12†	271	12.1	1.02	323	12.8	0.96	340	14.2	1.22	350
13*	111	8.3	0.88	297	12.6	0.90	208	13.6	1.02	130
14†	120	8.0	0.65	235	12.5	1.18	220	14.1	1.25	179
15*	120	10.6	0.90	260	13 8	1.27	242	11.4	0.92	185
Mean	135.1	10.2‡	0.93‡	252.7	12.1	1.02	252.9	13.1	1.08	210.9
		8.1§	0.74§							
Borderline diabetic "spike" curve										
16*	107	12.6	1.06	226	14.9	0.99	213	14.0	0.93	74
17†	90	6.1	0.58	195	12.0	0.98	179	10.8	0.95	86
18†	103	7.5	0.65	220	14.4	1.02	185	14.7	1.05	95
19†	105	12.0	0.93	235	19.7	1.63	173	17.6	1.17	95
20†	103	8.4	0.66	249	15.4	1.10	163	13.6	0.94	83
21*	115	11.6	0.94	190	15.1	1.30	176	15.5	1.40	111
22*	90	12.9	1.21	208	18.1	1.46	163	16.8	1.34	74
23*	111	10.4	1.05	213	17.6	1.81	125	11.0	1.35	70
24*	100	7.0	0.57	201	11.6	0.80	120	9.8	0.74	83
25*	109	11.4	0.77	193	12.9	0.58	76	9.2	0.36	78
Mean	103.3	11.0‡	0.93‡	213	15.2	1.17	157.3	13.3	1.02	84.9
		8.5§	0.71§							
Borderline diabetic "plateau" curve										
26†	83	8.9	0.81	195	11.6	0.87	195	9.5	0.55	179
27*	103	13.0	1.08	188	15.6	1.30	176	13.3	1.31	130
28*	102	7.0	0.66	168	12.3	1.05	185	14.3	1.04	90
29†	93	9.4	0.69	188	14.3	1.01	168	12.5	0.88	100
30†	103	5.3	0.55	168	10.8	0.67	163	12.0	0.76	95
31†	83	7.6	0.59	158	10.1	0.80	144	11.2	0.93	111
32†	90	5.8	0.36	158	11.0	1.05	149	12.6	1.00	78
33†	86	9.5	0.87	115	11.1	1.00	130	8.7	0.90	107
34*	115	7.9	0.74	193	10.8	0.92	185	11.9	0.92	139
Mean	95.3	9.3‡	0.83‡	170.1	12.0	0.96	166.1	11.8	0.92	114.3
		7.8§	0.65§							
Nondiabetic "normal" curve										
35*	105	8.9	0.78	153	11.1	0.98	100	7.5	0.70	111
36*	86	8.6	0.88	130	13.5	1.01	103	10.7	0.80	95
37*	98	8.7	0.79	133	14.4	1.12	66	9.0	0.96	78
38†	90	6.6	0.57	135	11.5	0.95	63	8.4	0.72	64
39†	90	7.7	0.89	144	13.9	1.11	66	11.6	0.94	74
40†	90	6.1	0.51	173	11.7	1.02	83	9.7	0.82	56
Mean	93.2	8.7‡	0.82‡	144.7	12.7	1.03	80.2	9.5	0.82	79.7
		6.8§	0.66§							
Nondiabetic "flat" curve										
41*	86	5.0	0.60	95	7.5	0.99	86	7.6	0.81	78
42*	115	10.0	0.80	102	13.9	1.06	102	11.1	0.78	70
43*	74	7.2	0.72	88	8.8	0.81	109	7.9	0.64	70
44†	88	10.1	0.89	111	15.0	1.30	86	9.2	0.91	72
45†	95	6.4	0.57	135	11.0	0.98	125	11.0	0.95	74
46*	90	11.7	1.01	107	16.1	1.39	88	10.2	0.82	78
Mean	91.3	8 5‡	0.78‡	106.3	12.1	1.09	99.3	9.5	0.82	73.7
		8.3§	0.73§							

*Patient rested thirty minutes in a chair before glucose was given.
†Patient rested sixty minutes in bed before glucose was given.
‡Mean for patients who rested thirty minutes in a chair.
§Mean for patients who rested sixty minutes in a bed.

CUSHING'S SYNDROME

The type of diabetes associated with Cushing's syndrome and the role of the adrenal glands in the metabolism of carbohydrate are of current interest. In 1934 Hartman and Brownell[18] showed that adrenalectomy would relieve diabetes in the experimental animal. In 1936 Evans[19] demonstrated that one activity of the adrenal cortex was to increase gluconeogenesis from protein. The subject was reviewed by Long, Katzin and Fry[20] in 1940. Later, Drury[21] showed that all of the excess glucose following the use of adrenal cortical extracts could not be accounted for by gluconeogenesis from protein, and that decreased oxidation of carbohydrate in the tissues was also a factor. Another facet of the problem was presented in the demonstration by Ingle and co-workers[6] of the marked insulin insensitivity of rats with adrenal cortical hyperfunction. Further study led to the concept of "steroid diabetes," which can be provoked in rats by the administration of 17-hydroxy-11-dehydrocorticosterone (cortisone) and 17-hydroxycorticosterone (compound F). This is characterized by relative insulin insensitivity, amelioration when food is withheld, negative nitrogen balance, and return to normal when administration of the hormone is discontinued.

Studies of blood lactate and pyruvate in Cushing's syndrome or in the "steroid diabetes" produced by the administration of cortisone or corticotropin (ACTH) have not been reported heretofore.

Standard glucose tolerance tests with concomitant determinations of lactate and pyruvate were performed on 11 patients with Cushing's syndrome. All these patients rested in bed at least one hour before the basal blood sample was drawn. The diagnosis was clinical. It was supported, however, in most instances by laboratory determination of hormone excreted (Table 2). All 11 patients underwent surgical treatment at some time during the course of their disease. Adrenal cortical adenoma was found in none and, therefore, all 11 have been classified as having so-called adrenal cortical hyperplasia.

Five of these 11 patients (cases 47-51 in Table 3) responded normally to the glucose tolerance test. They likewise showed no abnormality in the behavior of the levels of lactate and pyruvate. Six of the 11 (cases 52-57) however, responded with a "diabetic" type of glucose curve, and in 4 of them (cases 52-55) the basal (fasting) values for lactate and pyruvate and the subsequent levels of these metabolites exceeded what would be expected even in the nondiabetic or normal subject (Table 3). This excessive elevation of the levels of lactate and pyruvate seemed particularly significant in that the amount of glucose used by us (1 gm. per kg. of body weight) approximated only one-half of that given by Horwitt and co-workers[5] (1.8 gm. per kg. of body weight) in establishing the criteria of a normal response. In the fifth (case 56) of the 6 patients who had diabetic glucose tolerance curves, the response of the lactate and pyruvate was slightly subnormal, resembling that observed in the cases of borderline diabetes mellitus, while in the sixth, (case 57) that of a patient with Cushing's syndrome of six years' duration, the response was typical of more severe diabetes mellitus; namely, a relatively minimal increase of lactate and pyruvate when related to the marked increase of glucose.

COMMENT

The data collected in these studies supplement previous observations.[5] The smooth and proportionate responses of lactate and pyruvate to ingestion of glucose, typical of subjects with undisturbed metabolism of carbohydrate, and the delayed and proportionately smaller responses of these metabolites in cases of severe diabetes mellitus, were recognized previously. The degree of response in patients with mild and borderline diabetes mellitus falls between these two extremes. The transition from the so-called normal to abnormal is gradual, and no clear-cut line of demarcation is evident. Thus, under the conditions of this study, with the patient receiving no more glucose than 1 gm. per kg. of body weight, the curves for lactate and pyruvate apparently added little to the diagnostic value of the glucose curve alone, nor was light thrown on the pathogenesis of what disorder existed. In this regard, it should be mentioned that the "plateau" type of glucose tolerance curve is not only seen in cases of borderline diabetes mellitus but also is encountered frequently in cirrhosis of the liver, hyperthyroidism, hyperfunction of the adrenal glands, and after administration of cortisone or corticotropin.

Although estimation of the values for blood lactate and pyruvate under the conditions of this study appears to offer little of clinical usefulness in the diagnosis of diabetes mellitus, the smoothly graduated transition from normal to abnormal suggests that response of lactate and pyruvate to the administration of glucose probably represents qualitative evidence of insulin activity. Our lack of fundamental knowledge of the actual details of in vivo relationships of necessity invalidates present attempts to consider such data on a quantitative basis.

In regard to Cushing's syndrome, it seems not unlikely that the presence of a diabetic glucose tolerance curve

TABLE 2 Patients with Cushing's Syndrome: Symptoms and Signs

Symptom or sign	Case 47	48	49	50	51	52	53	54	55	56	57
Hypertension	+	+	+	+	+	+	±	+	+	+	+
Buffalo hump	0	+	0	0	0	+	+	+	+	?	+
Moon face	+	+	+	+	+	+	+	+	+	+	+
Plethora	+	+	+	+	+	+	+	+	+	+	+
Thick trunk, thin extremities	+	+	?	+	?	+	+	+	+	+	+
Purple striae	+	+	+	?	0	+	+	+	+	0	+
Bruising or poor wound healing	—	+	+	+	+	+	+	+	+	+	+
Amenorrhea	—	+	—	0	—	+	+	+	—	(Surg.)	±
Osteoporosis	+	+	+	+	+	+	+	+	+	+	+
Thin skin	—	+	0	+	+	+	+	+	+	+	+
Acne	0	+	0	0	0	+	+	+	+	+	0
Keratosis pilaris	+	0	0	0	+	+	+	+	+	0	0
Hirsutism and androgenic changes	—	+	+	?	—	+	+	+	—	+	+
Weakness	+	+	0	0	0	+	+	+	+	?	?
Diabetes	0	0	0	0	0	+	+	+	+	+	+
Lymphopenia	0	+	?	+	+	+	+	+	+	+	0
17-Ketosteroids, mg./24 hours	11.6 12.8 17.0	26.1	17.5 8.6	7.6 8.4	15.3 3.3	17.6	15.2	18.6 34.3	27.9 54.7 59.3	7.1 7.4	10.2 14.5 14.8
Corticosteroids mg./24 hours	1.57 0.92 1.97	0.72	1.18	0.87	1.45 0.92 1.45	1.95	0.64 1.42	1.28 2.65	3.36 12.64 13.8 15.0	0.84 1.61	1.16 2.06 1.31
Alkalosis with hypochloremia and hypokaliemia	0	0	0	0	0	0	0	0	+	+	0
Duration of symptoms, years	7 or 8 to 1945. Surgery, 1945. Recurrence 1 yr. during 1949	10	5	14	7	1½	1½	2	¼	2-3	6

+ = Present. 0 = Not present or normal. — = Not recorded.

TABLE 3 Concentrations of Blood Lactate and Pyruvate Determined During Standard Glucose Tolerance Tests: Patients with Cushing's Syndrome

(Values expressed in mg. per 100 ml. of blood)

Case	Basal level Glu.	Lac.	Pyr.	After administration of glucose: 60 minutes Glu.	Lac.	Pyr.	120 minutes Glu.	Lac.	Pyr.	180 minutes Glu.	Lac.	Pyr.
47	86	6.3	0.55	173	10.2	1.28	107	9.9	1.17	81	6.7	0.61
48	90	11.1	1.01	158	13.7	1.07	137	13.1	1.04	78	10.5	1.01
49	70	7.5	0.73	118	11.4	1.11	56	8.9	0.73	63	6.8	0.70
50	74	7.6	0.76	149	10.4	0.88	135	9.7	0.93	107	9.4	0.88
51	86	7.6	1.45	149	9.2	1.57	115	7.4	1.17	70	—	—
52	103	15.2	1.30	190	19.0	1.81	238	19.7	2.02	173	15.6	1.69
53	95	16.4	1.46	179	17.1	1.71	176	11.3	0.95	130	9.0	0.88
54	103	21.9	2.42	281	33.1	3.56	252	29.1	2.73	173	25.8	2.63
55	193	17.7	1.83	264	23.5	2.58	281	26.2	2.87	285	28.0	2.72
56	100	7.7	0.65	220	15.3	1.32	220	13.8	1.05	113	9.9	0.83
57	95	8.4	0.85	193	10.8	1.08	201	11.1	1.18	173	13.8	1.29

may at times reflect the severity of the pathologic process in the adrenal gland. The more severe the symptoms, the more abnormal the metabolism of carbohydrate may be. However, it seems that this is not always true. Elevation of the tolerance curve, when present, probably represents a summation of the degree of excess production of steroid hormone and the state of efficiency of the compensatory mechanisms. During this period of adjustment any resulting hyperglycemia might be expected to provoke hyperfunction of the islets of Langerhans. The role of diminished peripheral utilization of glucose has been stressed by Drury,[21] but its relationship to the levels of blood lactate and pyruvate is not known. The in vitro studies of Villee and Hastings[22] suggest several possibilities. In the meantime, the results obtained in the present study appear to support the concept of increased production of insulin by pancreatic islet tissue.

SUMMARY

The concentrations of blood lactate and pyruvate were studied in a series of 34 cases of mild and borderline diabetes mellitus during the course of standard glucose tolerance tests. This was a continuation of work previously reported.[5]

In patients with abnormal glucose tolerance curves suggestive but not conclusively diagnostic of diabetes mellitus, the responses of lactate and pyruvate also were equivocal in most cases. As with the curves for blood sugar, there seemed to be no sharp demarcation between the normal and the diabetic.

Of 11 patients with the clinical diagnosis of Cushing's syndrome associated with adrenal cortical hyperplasia, 6 had diabetic glucose tolerance curves. In 4 of the 6 the levels of blood lactate and pyruvate were markedly elevated before glucose was administered and rose promptly to yet higher levels after the glucose was given. This is in sharp contrast to the delayed and relatively small response observed in diabetes mellitus and justifies ascribing to the diabetes of the type encountered with Cushing's syndrome a designation such as "steroid diabetes" to distinguish it from the usual form of clinical diabetes, commonly called "diabetes mellitus."

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The Effect of Hypophysectomy On the Growth of the Islets of Langerhans

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There has been considerable discussion concerning whether or not the pituitary gland exerts a trophic influence on the endocrine pancreas. In most instances where a trophic effect has been established, removal of the pituitary leads to atrophy of the target organ. It would be expected that if the pituitary exerts an essential influence over the islets of Langerhans, these structures should atrophy when the pituitary gland is removed.

Removal of the pituitary gland was reported by Krichesky[1] to lead to an increase in the volume of the islets of Langerhans in relation to body weight in male rats. Adams and Ward[2] found an increase in the number of islets following hypophysectomy in the newt, but Koster[3] could find no specific changes in the islets after hypophysectomy in dogs. It seemed desirable to study further the effect of hypophysectomy on the volume or weight of the islets of Langerhans in order to establish with greater certainty whether or not hypophysectomy caused any appreciable change.

MATERIALS AND METHODS

Hypophysectomized female Wistar rats, and female and male Sprague-Dawley rats* weighing initially from 85 to 196 gm., together with intact control rats of the same strain, were used as the experimental animals. The rats were kept in individual cages. For the most part, the controls were paired-fed, but in some instances controls fed ad libitum were also used. The animals were sacrificed 28-125 days after operation. Islet weights were estimated by a slight modification of the method of Haist and Pugh.[4] Two different diets were used in these experiments. The first was ground fox chow. The second consisted of equal parts of milk, bread and canned dog food. The animals ate more of the latter diet.

*Obtained from Hormone Assay, Inc.

EXPERIMENTAL RESULTS

The effect of hypophysectomy on the islet weights in Wistar rats on a diet of ground chow for periods of 28-125 days is indicated in Table 1. Each hypophysectomized animal had its individual control which received the same caloric intake.

Table 2 presents the data on Sprague-Dawley rats kept for a period of 28 days on the special diet. Each hypophysectomized animal had its individual control receiving the same caloric intake. Control animals fed ad libitum were also used.

Table 3 shows the results of another experiment in which the hypophysectomized and control animals were

TABLE 1 The effect of hypophysectomy on the islet weights of rats on a chow diet (Hypox = hypophysectomized)

Strain	Group	Duration of Experiment (Days)	Body Weight Initial (gm.)	Body Weight Final (gm.)	Pancreas Weight (gm.)	Islet Weight (mg.)	Percentage of Islet Tissue in Pancreas	Islet Weight per 100 gm. Body Weight (mg.)
Wistar	Hypox	28	162	120	0.326	3.7	1.13	3.1
	P-F control	32	180	147	0.669	6.5	0.97	4.4
	Hypox	37	130	120	0.210	4.0	1.91	3.3
	P-F control	39	135	110	0.584	4.0	0.69	3.6
	Hypox	82	193	144	0.234	4.7	2.01	3.3
	P-F control	85	196	150	0.667	4.6	0.69	3.1
	Hypox	100	169	165	0.292	6.4	2.19	3.9
	P-F control	102	172	142	0.640	4.3	0.67	3.0
	Hypox	125	167	166	0.190	6.1	3.21	3.7
	P-F control	130	184	166	0.682	5.5	0.81	3.3
	Hypox	31	120	102	0.276	2.0	0.73	2.0
	Ad lib. control	122	122	150	0.690	7.7	1.12	5.1

Difference between hypophysectomized and paired-fed controls.
Islet weight: $t = 0$. Difference is not significant.
Percentage of islet tissue in pancreas; $t = 3.69$; difference is probably significant ($p < .022$).
Islet weight per 100 gm. body weight; $t = 0.054$. Difference is not significant.

TABLE 2 The effect of hypophysectomy on the islet weight of rats on the special diet (Hypox = hypophysectomized)

Strain	Sex	Group	Duration of Experiment (Days)	Body Weight Initial (gm.)	Body Weight Final (gm.)	Pancreas Weight (gm.)	Islet Weight (mg.)	Percentage of Islet Tissue in Pancreas	Islet Weight per 100 gm. Body Weight (mg.)
Sprague-Dawley	M	Hypox	28	90	84	0.334	3.7	1.11	4.4
	M	P-F control	28	90	60	0.440	4.3	0.98	7.2
	M	Hypox	28	88	104	0.228	3.9	1.71	3.8
	M	P-F control	28	88	100	0.544	4.7	0.86	4.7
	M	Hypox	28	102	98	0.232	2.9	1.25	3.0
	M	P-F control	28	96	90	0.542	5.3	0.98	5.9
	M	Hypox	28	87	98	0.251	3.2	1.28	3.3
	M	P-F control	28	87	94	0.499	4.7	0.94	5.0
	M	Hypox	28	87	98	0.334	4.1	1.23	4.2
	M	P-F control	28	87	84	0.506	4.4	0.87	5.2
	F	Hypox	28	92	114	0.229	3.4	1.49	3.0
	F	P-F control	28	92	122	0.585	3.7	0.63	3.0
	F	Hypox	28	98	112	0.218	3.4	1.56	3.0
	F	P-F control	28	98	130	0.591	4.0	0.68	3.0
	F	Hypox	28	90	104	0.244	2.4	0.98	2.3
	F	P-F control	28	92	122	0.647	3.0	0.46	2.5
	F	Hypox	28	92	114	0.245	3.3	1.35	2.9
	F	P-F control	28	92	122	0.563	3.7	0.66	3.0
	M	Ad lib. control	28	94	216	0.875	8.2	0.94	3.8
	M	Ad lib. control	28	86	226	0.919	8.4	0.91	3.7
	M	Ad lib. control	28	94	236	0.941	8.4	0.89	3.6
	F	Ad lib. control	28	104	220	0.832	5.7	0.69	2.6
	F	Ad lib. control	28	94	182	0.867	7.3	0.84	4.0
	F	Ad lib. control	28	100	230	1.024	7.8	0.76	3.4
	F	Ad lib. control	28	104	210	0.904	8.6	0.95	4.1

Differences between hypophysectomized and paired-fed controls.
Islet weights; $t = 3.62$. Difference is significant ($p < .01$).
Percentage of islet tissue in pancreas; $t = 5.72$. Difference is highly significant ($p < .001$).
Islet weight per 100 gm. body weight; $t = 2.75$. Difference is probably significant ($p < .05$).

Differences between hypophysectomized and controls fed ad libitum.
Islet weights; $t = 11.34$. Difference is highly significant ($p < .001$).
Percentage of islet tissue in pancreas; $t = 5.21$. Difference is highly significant ($p < .001$).
Islet weight per 100 gm. body weight; $t = 0.912$. Difference is not significant.

TABLE 3 The effect of hypophysectomy on islet weights; rats paired-fed by groups (Mean values are followed by standard deviations)

Strain	Sex	Group	No. of Rats	Duration of Experiment (Days)	Mean Body Weight Initial (gm.)	Mean Body Weight Final (gm.)	Mean Pancreas Weight (gm.)	Mean Islet Weight (mg.)	Mean Percent of Islet Tissue in Pancreas	Mean Islet Weight per 100 gm. Body Weight (mg.)
Sprague-Dawley	F	Hypox	4	30	106	100±5.3	0.310±0.006	3.7±0.74	1.19±0.25	3.7±0.6
	F	P-F cont.	4	30	99	123±12.9	0.663±0.074	4.5±0.78	0.69±0.16	3.7±0.76
	M	Hypox	4	30	96	97±3.8	0.313±0.034	3.4±0.19	1.08±0.11	3.48±0.24
	M	P-F cont.	4	30	92	120±6.14	0.577±0.061	4.1±0.13	0.72±0.08	3.48±0.21

Differences between hypophysectomized and controls disregarding sex.
Islet weights; $t = 2.95$. Difference is significant ($p < .02$).
Percentage of islet tissue in pancreas; $t = 5.5$. Difference is highly significant ($p < .001$)
Islet weight per 100 gm. body weight; $t = 0.112$. Difference is not significant.

paired-fed by groups, i.e. the amount of food eaten by each of the hypophysectomized animals was measured and an amount equal to the average of these values was then given to each of the control rats.

Table 4 presents information obtained in 10 additional hypophysectomized rats with no accompanying controls.

Analysis shows that in the tests presented in Table 1 there was no significant difference between the islet weights in hypophysectomized and paired-fed control rats. It is to be noted that in the hypophysectomized rats the islet weights reflect the body weights at the time of operation. The results included in Table 2 showed a significant difference in islet weights between hypophysectomized and paired-fed control rats ($p<.01$), the hypophysectomized rats having the smaller amount of islet tissue. This difference was less apparent when expressed in terms of body weight, but still probably significant ($p<.05$). In this table, too, it is evident that the islet weights in hypophysectomized rats are much less than in control animals fed ad libitum. Values for the two groups do not overlap. In the experiment in which the animals were not paired-fed individually, a significant difference in islet weights between hypophysectomized and control animals was also evident ($p<.02$). Expressed in terms of body weight the difference was not significant. In Figure 1, islet weights for 128 normal Wistar and Sprague-Dawley male and female animals obtained by seven different observers are presented. The regression line for these data $Y = 0.336x—0.05$) is also shown. On this chart are plotted also the values obtained in Wistar and Sprague-Dawley rats hypophysectomized for 23-125 days. It will be evident that the weights of the islets of Langerhans in hypophysectomized animals are very similar to the islet weights in normal animals of the same body weight.

The main reason for the differences in Tables 2 and 3 between hypophysectomized rats and their paired-fed controls is that the gain in body weight and islet weight

TABLE 4 Islet weights in hypophysectomized Sprague-Dawley rats

Sex	Duration (Days)	Final Body Weight (gm.)	Pancreas Weights (gm.)	Islet Weights (mg.)	Percentage of Islet Tissue in Pancreas	Islet Weights per 100 gm. Body Weights (mg.)
F	23	109	0.259	4.3	1.64	3.9
F	55	92	0.210	3.9	1.85	4.2
F	75	152	0.364	5.5	1.51	3.6
F	75	166	0.341	6.0	1.74	3.6
M	23	86	0.339	4.0	1.17	4.7
M	23	114	0.355	4.2	1.17	3.7
M	75	168	0.344	5.5	1.61	3.3
M	75	152	0.241	5.3	2.19	3.5
M	25	133	0.359	4.8	1.34	3.6
M	49	130..	0.279	3.0	1.08	2.3

in the paired-fed *control* group is greater than in the hypophysectomized animals. The differences then are not due to reductions in the islet weights in the hypophysectomized rats so much as to increases in the islet weights in control animals. In Table 1 the control animals did not gain weight and in this instance there was no significant difference in islet weights between hypophysectomized and paired-fed control rats. Figure 2 gives the mean values for islet weights in hypophysectomized rats, paired-fed control rats and control rats fed ad libitum. The pancreas weights in hypophysectomized and paired-fed control rats and the percentages of islet tissue in the pancreases in these two groups are also indicated. The islet-to-pancreas ratio is increased in the hypophysectomized rats in all experiments. This effect is due to the reduction in the total pancreas weight which is evident in Figure 2 and the tables. Figure 2 shows also that the islet weight per 100 gm. body weight is not much different for hypophysectomized rats, paired-fed controls and control rats fed ad libitum.

DISCUSSION

These experiments demonstrate that hypophysectomy prevents the growth of the islets of Langerhans but that within the periods studied, though there may be moderate differences between hypophysectomized and paired-fed control rats, no marked atrophy of the islets follows removal of the pituitary gland. However, the concentration of islet tissue in the pancreas is greatly increased. This is due to a great reduction in the weight of the pancreas as a whole, a change previously mentioned by Koster[3] and by Griffiths.[5] The finding of increased islet concentration emphasizes the fact that islet-to-acinar ratios may be misleading unless pancreas weights are also given, and that sections of pancreas may show an apparent increase in insular tissue, though the change is in reality a reduction in acinar tissue.

Haist,[6] on the basis of investigations on the insulin content of the pancreas in rats, concluded that there was no evidence for a normal regulation of islets by the pituitary gland. It was found that removal of the

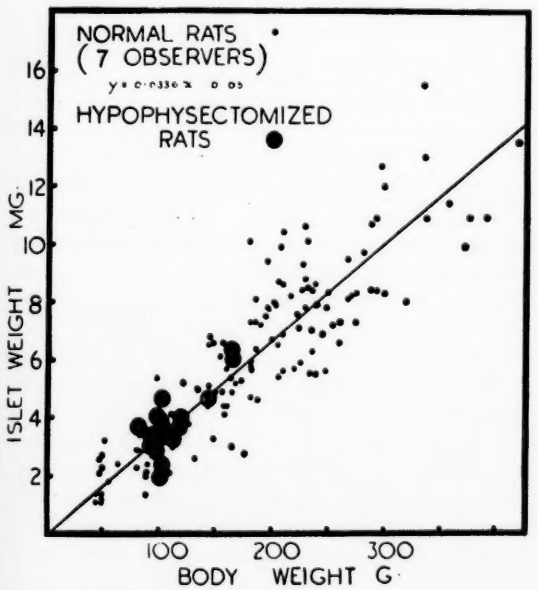

FIGURE 1 Comparison of islet weight in normal and hypophysectomized rats

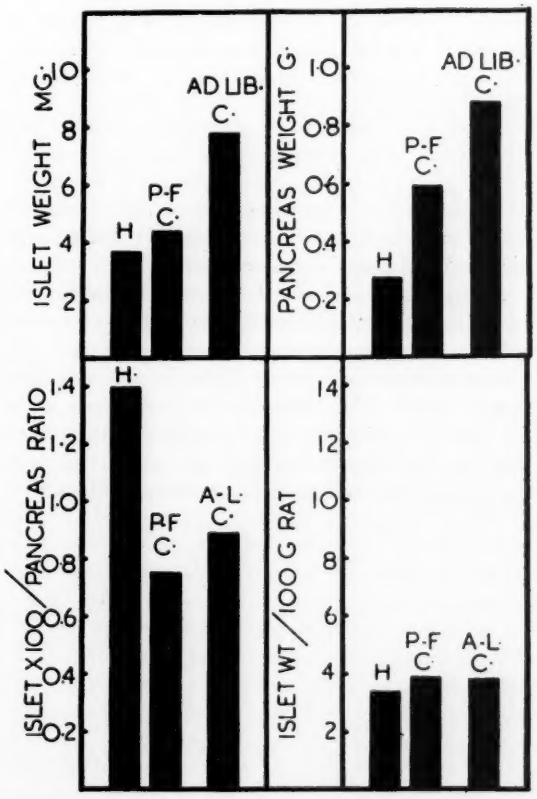

FIGURE 2 Summary chart for hypophysectomized rats (H), paired-fed controls (P-F C.) and controls fed ad libitum (Ad Lib C.)

pituitary gland led to no change in the insulin content of pancreas as compared to paired-fed controls, although the values were considerably less than in control rats fed ad libitum. Chambers, Sweet and Chandler[7] previously had reported that the insulin content of the pancreas in hypophysectomized dogs did not differ from that of control animals.

The results of the present study do not support the view that hypophysectomy leads to an increase in islet volume. They are harmonious, however, with the results of the insulin assays. The conclusion is that removal of the pituitary gland stops the growth of the islets as well as of the animal as a whole. While under some conditions a significant difference between hypophysectomized and paired-fed control animals may be obtained, the absence of marked islet atrophy such as occurs in the adrenals and gonads is against any fundamental trophic action of the pituitary gland on the islets. The reduction in the weight of the pancreas as a whole indicates that the pituitary exercises an important influence on the external-secreting portion of the gland. Whether this influence is direct or indirect, and what mechanisms are involved, is the subject of further investigation.

SUMMARY

1. The effect of hypophysectomy on the estimated weight of the islets of Langerhans in Wistar and Sprague-Dawley rats was investigated.

2. Hypophysectomy caused no marked atrophy of the islets. In the series in which the paired-fed control animals gained considerable weight there was a significant difference in islet weights between test and control groups. This difference was considered to be the result of an increase in islet weights in the control rats. The islet weights in hypophysectomized rats were significantly less than in control rats fed ad libitum.

3. The islet weight per unit of body weight did not show a consistent change as a result of hypophysectomy. The islet weights in hypophysectomized rats were similar to those of normal rats of the same body weight.

4. The weight of the pancreas was very definitely reduced following hypophysectomy. This led to a highly significant increase in the percentage of islet tissue in the pancreas (islet-to-acinar ratio) as a result of the removal of the pituitary gland, even though the islet tissue had not actually increased.

5. The conclusion is that the removal of the pituitary gland stops the growth of the islets but does not lead to marked islet atrophy, though the weight of the pancreas as a whole is reduced.

ACKNOWLEDGMENTS

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Spontaneous Recovery From Alloxan Diabetes In The Rat

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It has previously been suggested that there may be a general relationship between sulfhydryl compounds and the production of experimental diabetes[1]. In the course of a systematic study of this problem it was decided that an evaluation should be made of the effect of cysteine and methionine feeding on the development and progression of diabetes in the rat.

Foglia[2] has previously studied the effect of removal of 80 to 95 per cent of the pancreas in the rat and observed a progressive development of diabetes over the ensuing months. During the initial period following pancreatectomy, obesity was the only abnormal finding. During the next stage, classified as subdiabetes, abnormal blood sugar curves were found on glucose tolerance tests, but otherwise the blood sugar values were within the normal range. During the final stage with manifest diabetes, fasting hyperglycemia and glycosuria were present. The rate of the progression of the diabetes was proportional to the amount of the pancreas removed.

The present report deals with studies of the progression of diabetes in rats which were given one or more subthreshold doses of alloxan. Those rats which had an abnormal tolerance to glucose, but normal fasting blood sugar values (subdiabetes), were selected and followed in this study.

In the course of this study on the effect of feeeding sulfhydryl compounds to diabetic and subdiabetic rats it was found that many animals showed a spontaneous improvement in their disease after 12 to 20 months. This occurred in both the sulfhydryl-treated animals and in the untreated diabetic controls. A preliminary note on this work has been previously published[3].

METHODS

Male rats of both the Sprague-Dawley and Albino strain were used for these experiments. The alloxan was dissolved in distilled water at a concentration of 2 per cent and injected intravenously into the tail vein. Manifest diabetes was produced by injecting alloxan into non-fasted rats in doses of 35 or 40 mg. per kg.[4] When one to four injections of alloxan in doses of 30 mg. per kg. were administered, subdiabetes was produced. The repeated injections were given at two to five day intervals. All the rats showed abnormalities in the tolerance to glucose after they had received four injections of alloxan (30 mg. per kg.); occasionally a rat developed permanent diabetes after one or more injections. Many of the rats which received the 30 mg. per kg. dose of alloxan showed transitory hyperglycemia. However, the blood sugar usually returned to the normal range (100 to 150 mg. per 100 cc.) within a week after the last alloxan injection.

The samples of blood for chemical analysis were

*Aided by a research grant from the National Institutes of Health, Public Health Service No. A-20-C.

drawn about the same time each day, in the early afternoon. The blood sugar values were determined daily during the early period following the injection of alloxan. Later they were determined twice a week. The Folin-Malmros micro blood sugar method was used[5].

The rats were kept in metabolism cages. The urine was collected under toluene and the 24 hour excretion of glucose was determined. The urinary excretion of glucose was determined using the carmelization method of Somogyi[6]. The animals were fed a diet of proprietary dog food* in unlimited amounts. The diet contained 42 per cent carbohydrate, 24 per cent protein, 5 per cent fat, 4 per cent fiber, 13 per cent ash, and 10 per cent moisture. The water intake was restricted to a maximum of 160 cc. per day. The weight, food intake, and water intake were also determined daily. The average monthly values for body weight, blood sugar, etc. were determined and plotted on the graphs.

A glucose tolerance test was performed monthly on the subdiabetic rats. The following procedure was used. The rats were fasted for 16 to 18 hours and then given by intraperitoneal injection a 10 per cent solution of glucose in doses of 3.5 gm. per kg. of body weight. Serial samples of blood were drawn at the beginning and in, 1/2, 1, 2, 3 and 5 hours.

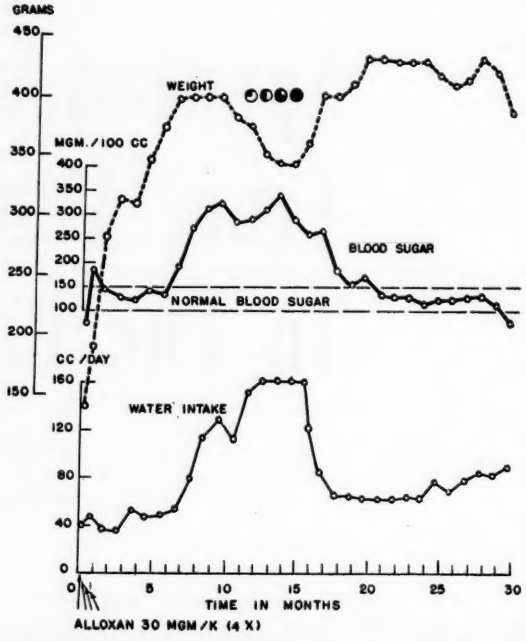

FIGURE 1 Progression and course of alloxan diabetes in the rat. (BB 83) Alloxan was injected in doses of 30 mg. per kg. on the 2nd, 4th, 9th, and 11th days. The stages of cataract development (+ to ++++) are represented by the partially filled circles over the weight curve

RESULTS

PROGRESSION OF DIABETES IN THE RAT. Figure 1 shows the progressive development of diabetes in a rat that had received four subthreshold doses of alloxan (30 mg. per kg. on the 2nd, 4th, 9th and 11th day). During the first few days following the alloxan injection, some of the blood sugar values were as high as 230. However, they returned to normal within a few days and between the second and sixth months the average monthly blood sugar values ranged between 120 and 145. This rat weighed 140 gm. at the time of the first alloxan injection and during the following six-month period it reached a weight of 400 gm. The observed gain in weight in this animal approximates the weight gain of normal rats. However, as shown in Figure 2 there was a progressive impairment of the glucose tolerance during this six-month period. From the sixth to the ninth months (see Figure 1) there was a progressive increase in the blood sugar, and values up to 350 were observed. Polydipsia, polyuria, and glycosuria appeared. The intake of water increased to 160 cc. per day. Associated with the onset of manifest diabetes, the rat lost 56 gm.

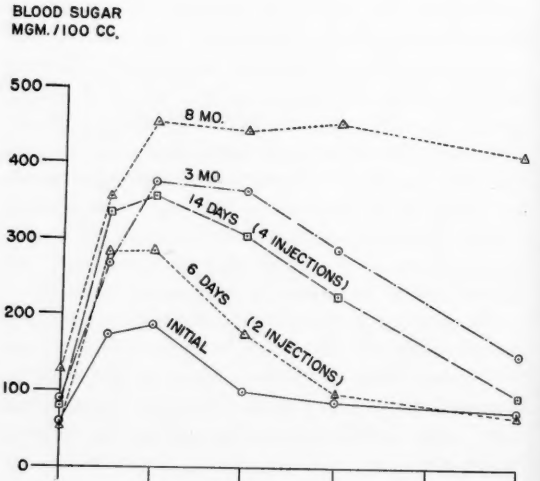

FIGURE 2 Progressive impairment in the tolerance to glucose in a subdiabetic rat (BB 83)

*"Friskies", Albers Milling Co.

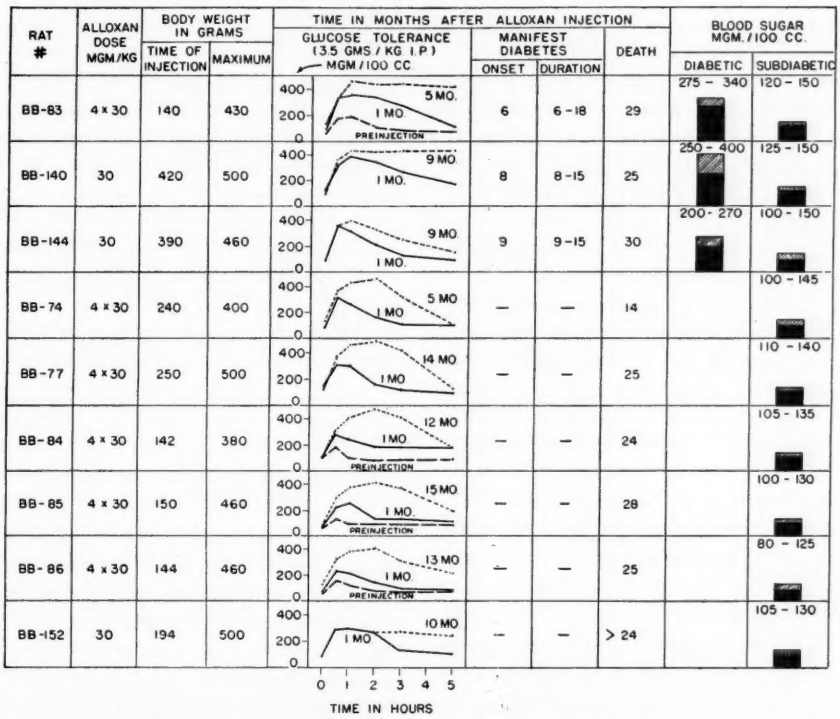
RAT #
ALLOXAN DOSE MGM/KG
BODY WEIGHT IN GRAMS
TIME OF INJECTION
MAXIMUM
TIME IN MONTHS AFTER ALLOXAN INJECTION
GLUCOSE TOLERANCE (3.5 GMS / KG I.P.)
MGM / 100 CC
MANIFEST DIABETES
ONSET
DURATION
DEATH
BLOOD SUGAR MGM. / 100 CC.
DIABETIC
SUBDIABETIC
BB-83 4 x 30 140 430 6 6-18 29 275 - 340 120 - 150
BB-140 30 420 500 8 8-15 25 250 - 400 125 - 150
BB-144 30 390 460 9 9-15 30 200 - 270 100 - 150
BB-74 4 x 30 240 400 — — 14 100 - 145
BB-77 4 x 30 250 500 — — 25 110 - 140
BB-84 4 x 30 142 380 — — 24 105 - 135
BB-85 4 x 30 150 460 — — 28 100 - 130
BB-86 4 x 30 144 460 — — 25 80 - 125
BB-152 30 194 500 — — > 24 105 - 130
5 MO.
1 MO.
PREINJECTION
9 MO.
1 MO.
9 MO.
1 MO.
5 MO
1 MO
14 MO
1 MO
12 MO
1 MO
PREINJECTION
15 MO
1 MO.
PREINJECTION
13 MO
1 MO
PREINJECTION
10 MO
1 MO
400
200
0
0 1 2 3 4 5
TIME IN HOURS

FIGURE 3 Progression of diabetes in a group of 9 subdiabetic rats. The blood sugar values are indicated in the last two columns. The cross hatched area represents the range

in body weight. Bilateral cataracts appeared beginning about the 12th month and by the 15th month, both lenses were completely opaque.

Of the nine subdiabetic rats studied, 33 per cent developed manifest diabetes, indicated by hyperglycemia, glycosuria and loss of weight, during the first year (see Figure 3). Although all of the remaining six rats showed a progressive impairment in the tolerance to glucose, none of these developed manifest diabetes during the period of survival (14 to 28 months). Figure 3 shows a comparison of the most abnormal glucose tolerance for each rat with that observed one month after the alloxan injection. Progressive impairment in the tolerance to glucose is evident in every case. During the second year following the injection of alloxan, all of these subdiabetic rats showed an improvement in their tolerance to glucose; the details of this amelioration will be discussed later. It should be noted that the development of manifest diabetes occurred in two rats (BB-140 and BB-144) which were nearly fully grown (390 to 420 gm.) at the time they were injected with alloxan, whereas manifest diabetes did not develop in some of the subdiabetic rats (BB-84, BB-85, or BB-86) even though they weighed only 140 to 150 gm. at the time the alloxan was injected.

SPONTANEOUS RECOVERY FROM DIABETES has been observed during the second year of the disease. In the case illustrated in Figure 4 the rat became diabetic after receiving one injection of alloxan (35 mg. per kg.). During the first year following the alloxan injection, the blood sugar ranged between 375 and 450. The body weight was 220 gm. at the time of injection and after one year the animal had attained a body weight of 254 gm. Marked glycosuria and polyuria were present and the water intake was maintained at 160 cc. per day. Beginning at about twelve months, amelioration of the diabetes appeared. During the following three-month period, the blood sugar returned to normal and remained normal for the succeeding 12 months. The animal began to gain weight rapidly, and over the succeeding months the body weight almost doubled. The polyuria, polydipsia and glycosuria disappeared completely. Although by 16 months the blood sugar had returned to normal (see Figure 5), the tolerance to glucose was still abnormal at this time. However, there was a progressive

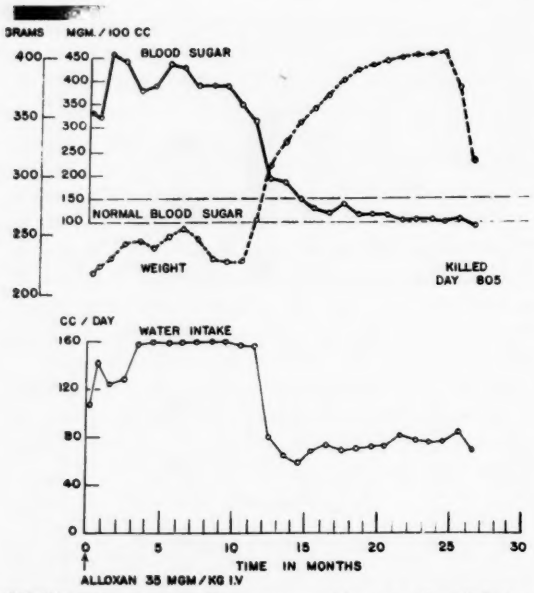

FIGURE 4 Spontaneous disappearance of long standing diabetes in the rat (BB 109)

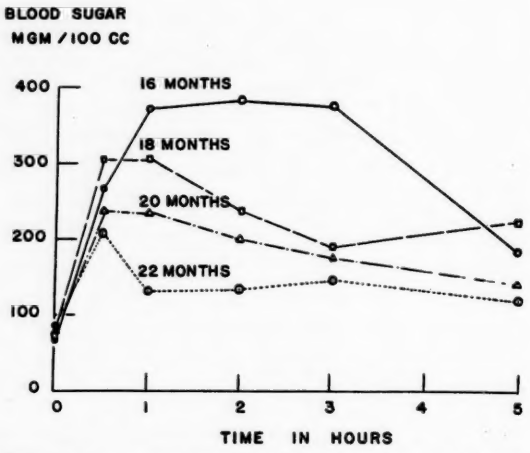

FIGURE 5 Progressive improvement in the tolerance to glucose (Rat BB 109)

improvement in the tolerance to glucose during the succeeding months and by 22 months the glucose tolerance test was normal; it remained normal during the succeeding months.

In the case illustrated in Figure 1, the rat was subdiabetic during the first six months following the alloxan injection, and diabetic from the 7th to the 17th months. This animal likewise showed spontaneous recovery from the diabetes. At about the 16th month the rat began to gain weight, and correspondingly there was a progressive decrease in the blood sugar values. By the 17th month the rat had regained all the lost weight. By the 21st month the blood sugar had returned to normal and it remained normal for the succeeding ten months (110 to 135). Polydipsia, polyuria and glycosuria likewise disappeared. The tolerance to glucose slowly returned to normal and by the 29th month, it had nearly returned to its pre-injection level.

Excluding the acute deaths occurring within the first week, somewhat less than half the rats suffering from diabetes (produced by injecting alloxan in doses of 35-40 mg. per kg. intravenously) died within the first year. The sixteen diabetic animals that survived for more than a year without treatment were studied. Of these, six rats died between the 12th and 14th months, and only one rat (17 per cent) showed an amelioration of the diabetes (see Table 1). A second rat, which was not included in the ameliorated group in which there was amelioration

TABLE 1 AMELIORATION OF MANIFEST DIABETES IN THE RAT

No. Rats	Months of survival	Amelioration of the Diabetic State			Blood Sugar MG/100 CC	
		Per cent of animals	Time of onset in months	Duration in months	Tests in individual rats in the diabetic state	Range of tests after amelioration
6	12-14	17 (33%)**	13	1	350, 600, 400, 390, 600, 350	125
4**	16-19**	75***	9-19	1-7	220, 500, 375, 600	120-125
6	22-30	100	13-20	3-13	325, 300 200, 400, 300, 300	100-150

* One rat was beginning to show amelioration at the time of death.
** Three of these animals are still living.
***The fourth rat which is still living is beginning to show an improvement in the diabetic state at 19 months.

was just beginning to show signs of improvement at the time of death. Of four diabetic rats followed for 16 to 19 months, 75 per cent showed amelioration of their disease. The fourth animal in this group is still alive at 19 months; it is beginning to gain weight and show a decrease in glycosuria. Of six diabetic rats that survived 22 to 30 months, 100 per cent have shown amelioration of the disease. Amelioration of the diabetic state began after 13 months and before 20 months in nine of the ten animals; only one rat showed amelioration in less than one year (9 months).

SPONTANEOUS IMPROVEMENT IN THE TOLERANCE TO GLUCOSE IN SUBDIABETIC RATS In the six subdiabetic rats that did not develop manifest diabetes (Figure 3), there was a progressive improvement in the tolerance to glucose during the second year of the disease (Figure 6). The blood sugar values of the "most abnormal" and the "most normal" glucose tolerance test (after amelioration) are plotted in Figure 6. It should be noted that although an improvement in the tolerance to glucose was noted in all cases, it did not occur in less than a year and in some, it occurred as late as 21 months after the alloxan injection.

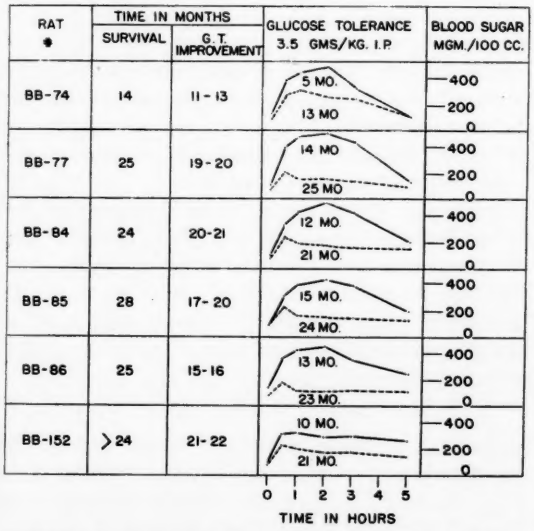

FIGURE 6 Spontaneous improvement of the tolerance to glucose in the subdiabetic rat

COMMENT

PROGRESSION OF DIABETES IN THE RAT Our findings on the progression of diabetes in the rat following subthreshold doses of alloxan are in qualitative agreement with the previously reported studies of Foglia which were carried out in the partially depancreatized rat.[2] As judged by changes in the tolerance to glucose, all rats showed a progression in the diabetic state during the first year of the disease. Our results differ quantitatively from those of Foglia in that only 33 per cent of 9 rats developed manifest diabetes, whereas most of the partially deprancreatized rats became diabetic. Although vaiations in the composition of the diet influence the rate of progression of diabetes in the partially depancreatized rat,[7a-b] it is probable that the quantitative difference observed in the incidence of manifest diabetes cannot be attributed to dietary factors. However, a careful study is now being made to evaluate the effect of diet on the progression of diabetes in the alloxan-injected animals; these observations will be reported at a later date.

When manifest diabetes did develop it appeared within six to nine months following the alloxan injection. The diabetes was of moderate severity; in some cases the afternoon blood sugars reached a height of 400; the 24 hour glucose excretion reached values of up to 6 gm. per day. Rats made subdiabetic by injecting alloxan differ from partially depancreatized rats in two important respects. Depancreatized rats have a diminished exocrine secretion of the pancreas; this in turn may influence the rate of digestion and absorption of foodstuffs. Partially depancreatized rats would also be expected to have a diminished secretion of the hyperglycemic factor which is presumably formed by the alpha cells of the pancreas.[8,9] However, it would be difficult to attribute the quantitative differences observed to these factors.

It is possible that the progression of the diabetes in the alloxan-injected rat may be masked by the simultaneous operation of the amelioration factor. Although the effects of the amelioration factor are apparent during the second year of the disease, this factor may also be operating during the first year. Thus the appearance of manifest diabetes would be dependent upon the relative rates at which these two opposing processes develop.

The progression of diabetes in rats injected with a subthreshold dose of alloxan parallels, fairly closely, the development of human diabetes. Human patients with mild diabetes may have a decreased tolerance to glucose and a normal postprandial blood sugar value. These cases may then progress and show weight loss, hyperglycemia, glycosuria, polydipsia and polyuria.

CAUSES OF THE PROGRESSION OF DIABETES Certainly the development of manifest diabetes in the rat six to nine months after the injection of alloxan cannot

be attributed to an effect of the alloxan injection per se. It might be argued, however, that in the period immediately following the alloxan injection the pancreas was capable of secreting almost enough insulin to supply the body's needs, but that with the growth of the animal, the need for insulin exceeded the secretory capacity of the beta cells, and hence manifest diabetes developed. In this connection it is of interest to note that two of the three rats which developed manifest diabetes had reached maturity (body weight 390 to 400 gm.) prior to the alloxan injection, whereas many of the subdiabetic rats which did not develop manifest diabetes quadrupled their body weight after the alloxan was injected (see Figure 3).

The observed progression of diabetes in the alloxan-injected rat is compatible with the hypothesis that (1) specific chemical, hormonal, or toxic agents are present within the normal organism and that (2) these agents are capable of producing progressive damage to the insulin-producing cells. If the pancreatic reserve is diminished, as is the case in the rat which had received a subthreshold dose of alloxan, these agents are capable of producing manifest diabetes. Similar chemical, hormonal, or toxic agents might likewise play a role in the etiology of human diabetes. However, one cannot exclude the possibility that factors outside the pancreas may contribute to the observed progression of the diabetes in the rat.

AMELIORATION OF THE DIABETES To date our results indicate that all alloxan-diabetic animals will show spontaneous amelioration of their disease if they survive for more than 20 months. Amelioration is rarely observed prior to one year and it may begin as late as 20 months. Although it is true that rats with severe diabetes are apt to die in less than a year, some rats with severe diabetes, indicated by blood sugar values as high as 600, have lived for more than a year. Insulin was not given to any of these animals. The time at which amelioration of the diabetes develops appears to show greater correlation with the duration of the disease than with the severity of the diabetes. Subdiabetic rats show an improvement in their tolerance to glucose at about the same time that rats with manifest diabetes show return of the blood sugars to normal. Amelioration has been observed in two strains of rats (Albino Farms and Sprague-Dawley).

In considering the cause or causes of the spontaneous disappearance of the diabetes, it is helpful to consider the interplay of the various endocrine glands illustrated in Figure 7. The recent work in experimental diabetes[1]

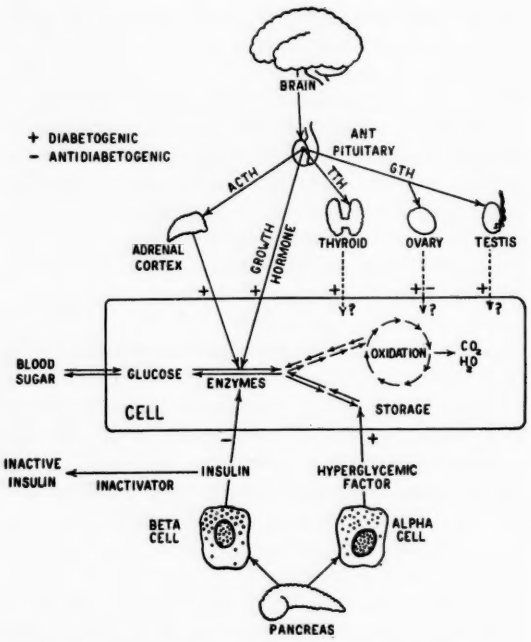

FIGURE 7 The role of the endocrine factors in diabetes

clearly indicates that diabetes is not due to a simple insulin deficiency but that it results from an endocrine imbalance between insulin on the one hand and growth hormone, compound F, thyroxine, and other factors on the other. Although the removal of the pancreas will cause diabetes,[10] the subsequent removal of the pituitary gland[11] or the adrenal cortex[12-14] will ameliorate the diabetes. Obviously these latter procedures cannot restore the secretion of insulin in a depancreatized animal. Furthermore, the injection of excessive amounts of growth hormone,[15-17] or compound F,[18] into an animal with a normal pancreas likewise produces an endocrine imbalance, and diabetes.

BETA CELL REGENERATION AND AMELIORATION In the diabetes which follows the injection of alloxan there is an endocrine imbalance due to insulin deficiency,[19] for alloxan selectively destroys the beta cells of the pancreas.[20] The most obvious explanation for the amelioration of the diabetes would be a regeneration of the beta cells in the pancreas. If this were the case, one might ask why beta cell regeneration begins only after a year or more. Furthermore, one might expect that a progressive regeneration of the beta cells would produce an early improvement in the subdiabetic rats. However, it

has been observed that the blood sugar value of rats with manifest diabetes returns to normal at about the same time that the subdiabetic rats show an improvement in their tolerance to glucose. Detailed histological study of the tissues of these rats is underway but as yet these studies are incomplete. Although the islets examined so far do not show obvious evidence of beta cell regeneration, final decision on this point will have to await the quantitative determination of the numbers and volumes of the beta cells in the pancreas of these animals at various times following the injection of alloxan. A beta cell adenoma was found in the pancreas of two of the rats. The nodules were encapsulated; they consisted of cords of epithelial cells. These contained large numbers of intracellular granules which stained intensely with Gomori's aldehyde fuchsin stain.[21] Although it would seem unlikely that all of the rats showing amelioration develop islet adenomas, this possibility cannot be excluded until the complete pancreas is studied in serial section.

In 1948, Young reported one case of spontaneous disappearance of diabetes in a cat with metahypophyseal diabetes.[22] This animal developed permanent diabetes which persisted after the injections of anterior pituitary extract were discontinued. Beginning at about the fourth month the glycosuria began to slowly fall, and the body weight, which had declined, began to rise again. After eight months, the urine became sugar free. The cat was killed eleven days after the urine had become sugar free. On exhaustive histological examination of the pancreas, Richardson[23] was "unable to find evidence for the existence of any beta cell which had not undergone extreme hydropic degeneration". These results would suggest that the amelioration of the diabetes may be due to extrapancreatic factors.

POSSIBLE ROLE OF OTHER FACTORS Amelioration of the diabetic state without altering the amount of available insulin might be the result of decreased functional activity of the pituitary or the adrenal gland. This would tend to restore the endocrine balance toward normal. Unfortunately, very little is known about the quantitative variations with age in the secretion of the growth hormone or adrenal cortical steroids. Estrogens,[24,25] and androgens,[24,26] are reported to have diabetogenic effects in experimental animals. Since the functional activity of the sex glands decreases with age, it is possible that a decreased androgen function could contribute to the amelioration of the diabetic state. Atrophy of the testes had been found in the present studies, but this atrophy may be an associated phenomenon rather than a causative factor. Since the secretion of a hyperglycemic factor by the alpha cells of the pancreas may contribute to the diabetic state,[9] it is possible that a secondary exhaustion or diminished activity of the alpha cells could contribute to the amelioration of the diabetic state.

The concentration of insulin within the body depends upon the relative rates of insulin synthesis and destruction. Since insulin can be inactivated by an enzymatic factor present in the blood and the tissues,[27,28] variations in the rate of insulin destruction would influence the diabetic state. If the ability of the rat tissues to inactivate insulin were to decrease after one or two years of diabetes, this factor could contribute to the amelioration of the disease.

Lastly, it should be emphasized that the basic biochemical reactions in the tissues take place in the absence of insulin and the other hormones; the endocrine glands merely govern the relative rates and direction of these biochemical reactions. The rates of these reactions are also controlled by the concentration of the various enzymes and coenzymes within the cell, by the availability of substrates, etc. Thus the presence of a functioning liver is necessary for the maintenance of hyperglycemia in the diabetic animal.[29] It is possible, therefore, that the liver and other tissues, too, may show quantitative differences in their requirements for the various hormones at different ages, and thus contribute to the amelioration of the diabetic state.

JUVENILE VERSUS ADULT TYPES OF DIABETES It is generally agreed that human diabetic patients may be separated into two types of diabetes — juvenile (or labile) and adult (or stable) types. The former show wider fluctuations in blood sugar values and they require larger doses of insulin for control. It has been suggested that these two types of diabetes may represent two different disease entities.[30] The amelioration of the diabetes in the rat which takes place late in life makes one wonder whether the two types of human diabetes may represent the variations in the response of the organism to the same disease entity at two different ages.

These observations on the spontaneous amelioration of diabetes could be interpreted to mean that alloxan diabetes in the rat is different from its human counterparts because the latter rarely show such spontaneous improvement in their disease. If this were the case it would be prudent to cease work on this problem and turn to other more productive fields. As an alternative, it is possible that if one can determine the cause of the spontaneous amelioration of diabetes in the rat, it may also be possible to induce a similar amelioration in man.

Being an optimist by nature, I prefer the latter interpretation.

SUMMARY

A subdiabetic condition indicated by abnormal glucose tolerance and normal postprandial blood sugar was produced in rats by injecting one to four doses of alloxan (30 mg. per kg. intravenously). All the subdiabetic animals show a progressive impairment in tolerance to glucose during the first year of the disease. Within the first year following the alloxan injection, 33 per cent (three out of nine) of the subdiabetic rats developed manifest diabetes, manifested by blood sugar ranging from 200 to 400 mg. per 100 cc.

Spontaneous amelioration and complete disappearance of diabetes occurred during the second year of the disease. In animals which have maintained continuous hyperglycemia (200 to 600) for over a year, the blood sugar returned to normal (100 to 150) and remained normal. Amelioration rarely began prior to one year and it sometimes began as late as 20 months. The tolerance to glucose returned to normal some months after the blood sugar had returned to normal.

One of six diabetic rats that survived for 12 to 14 months showed an improvement in the disease. Nine of ten diabetic rats that survived for 16 to 30 months showed amelioration of their disease. The tenth rat in this group is still alive at 19 months and it is just beginning to show a progressive decrease in glycosuria.

One hundred per cent of six subdiabetic rats showed amelioration in their tolerance to glucose during the second year of the disease. This amelioration leads to speculation regarding the possible induction of similar amelioration of diabetes in man.

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DISCUSSION

DR. ALEXANDER MARBLE (*Boston*): Dr. Lazarow's findings are of great interest even though at present their interpretation is difficult. Although their direct application to diabetes in man is not possible, they cause the clinician to pause and consider what evidence he has seen of amelioration or cure in human patients. One recalls quickly, evidences of apparent improvement which takes place in carbohydrate tolerance. It is common to find that patients improve after having been under treatment with a restricted diet and insulin for some days, weeks or months. In such patients as time goes on insulin may be lowered in dosage and at times discontinued. This happens most frequently in middle-aged, obsese individuals who on a restricted diet lose weight to a level more nearly proper for age and height. Indeed, in the past, some have been tempted to classify such patients as not having had diabetes at all but as having suffered from "hyperglycemia associated with obesity." Experience has taught that one must be cautious in this regard: later on, if excessive weight is regained or febrile complications occur, diabetes again may become manifest.

In children, one occasionally sees a remarkable effect with aggressive treatment early after onset. If a child is seen with marked hyperglycemia and glycosuria shortly after a fulminating onset of symptoms and if large doses of insulin are given in the first days of treatment, occasionally normal conditions are re-established so nearly that even though insulin is discontinued, the urine remains free from sugar and random blood sugar values are normal or nearly so. Only by a glucose tolerance test can diabetes be demonstrated. In such a situation the unwary physician is tempted to discontinue insulin entirely. However, experience has shown that it is better to continue insulin even in token dosage since the diabetes invariably reasserts itself after an interval of days or weeks. This marked amelioration has caused some of us to wonder whether the situation may be analogous to that in which pituitary diabetes in animals can be arrested by the use of insulin or a restricted diet.

In addition to these examples of amelioration of human diabetes, one encounters the rare case in which undoubted diabetes has at one time apparently been present but later on cannot be demonstrated. However, these are rare situations which usually close scrutiny or the passage of time will clarify. Certainly, at present, no clinician would boast of a cure in human diabetes. What, then, of the situation which Dr. Lazarow has encountered in alloxanized rats? The amelioration or perhaps cure of this form of diabetes comes after some 12 to 20 months. If the cause for improvement lies outside the pancreas, one has no evidence at present for such. If it lies within the pancreas, one wonders about regeneration of beta cells. Continuance of his work in the histological examination of islet tissue of the rats not only at late stages but also at varying intervals in the process of recovery may give the answer. Perhaps the insular adenomas which he has found in two animals may be a common finding. As for the human, we know that evidences of regeneration of beta cells are only rarely seen despite the fact that multiplication of such cells is possible as shown by the development of islet cell hyperplasia or definite tumors in certain individuals. In a practical sense, we can conclude that beta cell regeneration in man either takes place very little or is stopped in its very early stages since spontaneous cures of diabetes are rarely if ever encountered.

This train of thought leads to a consideration of the general problem of regeneration. One knows that this varies from tissue to tissue and from species to species. Thus connective tissue regenerates with great ease whereas nerve cells apparently do not regenerate after their final pattern has been set by at least two years of age. Heart muscle regenerates poorly. As for the influence of species, the rat has much greater capabilities in this regard than certain other animals, being able to regenerate lung or liver tissue if a relatively small portion of the organ is left intact. Hence caution must be used in transferring findings and conclusions in the rat to man.

The subject is fascinating and full of possibilities. We shall all await with great interest the results of Dr. Lazarow's studies in the future.

DR. JEROME W. CONN (*Ann Arbor, Mich.*): We have had an unique opportunity to follow a human being for five years after treatment with alloxan which was given in the hope of checking hyperinsulinism.* Fasting hypoglycemia persisted. Operation was then performed and an islet cell tumor was removed from the pancreas. It was found that the tumor had not been affected by

the alloxan but biopsy of the pancreas proper showed marked destruction of the beta cells of the islets.

For the past five years the patient has had glucose tolerance tests at intervals of six to nine months. During the first two years the tests showed increasing abnormality, but in the past three years there has been progressive improvement in carbohydrate tolerance. The patient has not had insulin or a diet. Fasting blood sugars have been normal. The glucose tolerance test is still diabetic in type after five years but is definitely improved.

Two years in the rat is relatively longer than five years in the human being. We shall be interested in finding out what happens in the next five years.

*Conn, J. W., and Hinerman, D. L.: Effects of alloxan upon function and structure of normal and neoplastic pancreatic islet cells in man. Am. J. Path. 24:429-49, March 1948.

DR. HENRY T. RICKETTS (*Chicago*): In a series of dogs with alloxan diabetes studied in a long-term experiment over a number of years, we found one animal entirely resistant to repeated doses; after a year to 18 months, glycosuria appeared and finally full-blown diabetes developed, with the excretion of 80 to 100 gm. of glucose per day in the urine. Conversely, in a number of cases of alloxan diabetes the animals have shown—in agreement with Dr. Lazarow's findings—a diminution in the severity of diabetes as the years have gone by. So, in the species of the dog, as well as in the rat, the same phenomenon may occur.

DR. ARNOLD LAZAROW (*Closing*): Studies of the histological changes in the endocrine glands of these animals are as yet incomplete; some of the rats are still alive. Although it seems improbable that a beta cell adenoma would have developed in all the animals that have recovered from their diabetes, this cannot be excluded until the pancreas is studied in complete serial section.

In order to estimate the secretory capacity of the pancreas it will be necessary to determine the insulin content of the pancreas as well as the number and the volume of the beta cells. Although the Toronto group has studied the total volume of the islet tissue in the rat, more refined methods will be needed to determine the beta cell component. Methods are being worked out which may permit this determination. It might be reemphasized that in the case of spontaneous amelioration of pituitary diabetes in the cat (reported by Young), Richardson had made an exhaustive histological study of the pancreas and found that of the few beta cells that remained in the pancreas, all showed extensive hydropic degeneration. The significance of this hydropic degeneration in the beta cell is not clear since Duff and others have recently shown that hydropic degeneration is really glycogen infiltration.

We are anxious, of course, to evaluate the histological status of the adrenal, pituitary, and various other endocrine organs. However, it may be that these morphological studies may not provide the desired clue. It may be more important to study the functional activities of the pituitary, the adrenals, and other endocrine glands at various times before and after the recovery from alloxan diabetes. Any suggestions as to methods approaching this problem will be appreciated.

I was very much interested to learn that Dr. Conn and Dr. Ricketts are finding similar recovery from alloxan diabetes in man and in the dog.

It should be emphasized that these rats which have shown spontaneous recovery from diabetes have not received any insulin treatment. It may be that the stimulus of the untreated diabetic state may be necessary to bring about the interplay of the factors that produce amelioration. It must be remembered that one year in the life of a rat would correspond to about 25 years in man as far as the relative life spans are concerned. Therefore, the diabetes in the rat cannot be strictly compared with the diabetes of human patients who have been treated with insulin.

Diabetes Mellitus In Puerto Rico

STATISTICAL SURVEY OF 700 CASES

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Diabetes mellitus as a disease entity has long been neglected in Puerto Rico. A review of the literature fails to reveal any comprehensive studies on this subject. In view of the scarcity of information of local origin we decided to analyze the histories of cases of diabetes from which a maximum of valuable information could be obtained.

The 700 cases presented in this report were collected from the University Hospital, the Presbyterian Hospital, the San Juan City Hospital and the private practice of the senior author.[1] Included were 700 cases, most of them from the University Hospital, in which treatment occurred prior to our connection with this institution. In many other cases, patients who were under our care at one time or another were referred back to the family physician in different towns of the island. These factors account for the relatively large number of "undetermined" items in our tables, particularly in relation to the follow-up. Most of the records, however, contain enough data to make their inclusion worthwhile, especially with regard to sex and age distribution, family history and type of diabetes and complications.

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ANALYSIS OF DATA

Sex Incidence

Two thirds of the diabetic patients in this series were female (Table 1). The sex distribution was almost identical with that found by John.[2] The percentage of female patients was greater among charity patients. This, we believe, is in great part due to the higher percentage of women attending the clinics of the abovementioned hospitals.

Age Distribution

The distribution, by decades, of the age at onset of the disease in our cases is included in Table 2 in addition to information compiled from the literature. It reveals a maximal incidence during the fifth and sixth decades tapering off towards both extremes of life. It is noteworthy that although the peak of distribution in most series also corresponds to the fifth and sixth decades,

there is in the present one a relatively lower incidence in the first three decades. The difference is more significant when it is realized that there is a higher proportion of younger people in the general population of Puerto Rico than in that of the United States and Western Europe where most of the data for similar statistical reports have been obtained.

Family History

In spite of the notorious unreliability of medical histories obtained from patients, especially those of the lower education level, a history of diabetes among the immediate relatives was elicited in 159 (24.5 per cent) of 648 cases in which such information was obtained.

Type of Onset

Information as to the type of onset could be obtained in only 443 cases (Table 3). It was gradual in 331 and rapid (less than one month) in 112. When these figures are analysed according to the age at onset, we find, as expected, that the onset was rapid in 53.6 per cent of those developing the disease before the age of 30, and in only 27.7 per cent of those 30 or over.

Type of Diabetes and Nutritional Status at Onset

In 555 cases about which there was adequate information, the diabetes was mild in 367 cases (66.1 per cent), moderately severe in 117 cases (21.0 per cent), while in the remaining 71 (12.9 per cent) it was severe; in 6 of these it was extremely difficult to control.

The nutritional status at onset of diabetes could be ascertained in only 623 cases. Of these there was excess weight in 402 (64.5 per cent), normal weight in 151 (24.2 per cent) and underweight in only 70 (11.3 per cent).

A correlation of the type of diabetes with the nutritional status at onset in both groups under and over 30 years of age is attempted in Table 4. It may be seen at a glance that mild diabetes with obesity predominates in the group over 30, while severe diabetes with underweight or normal weight is far more common among the younger people. These findings agree with the observations of most investigators.

Degree of Control and Type of Treatment

Any evaluation of the degree of control of diabetes involved serious difficulties. What is meant by "control of diabetes" must first be defined. We adopted the following criteria:

1. Diabetes is well controlled when there is optimal nutritional state, ideal weight, absence of glycosuria, and the blood sugar under 180 to 200. When dealing with juvenile or severe ("brittle") diabetics, the standards are more lax, since occasional and even frequent glycosuria will be accepted in order to prevent hypoglycemic attacks.

2. Fairly well controlled diabetes is shown by a fairly good weight and nutritional state but with lapses of hyperglycemia and glycosuria.

3. Finally diabetes is poorly controlled whenever there is failure to meet the above standards except when the patient is treated in the hospital under ideal conditions of supervision.

Following these criteria we were able to evaluate 637 cases as follows: In 291 (45.6 per cent) the diabetes was well controlled; in 207 (32.5 per cent) it was fairly well controlled; and in 139 (21.9 per cent) it was poorly controlled. In the last group, of course, were the six cases of uncontrollable ("brittle") juvenile diabetes mentioned above. We believe that the number of poorly controlled cases is relatively low considering the fact that a total of 161 follow their diet very poorly and 57 of these do not take their insulin regularly (Table 5).

Regarding the type of treatment, information was available in 677 cases. In 242 (35.8 per cent) diet only was employed; in 327 (48.2 per cent) insulin was used in addition in a dosage up to 40 units daily, and in 108 (26 per cent) over 40 units daily. Needless to say, the requirement of insulin was greater than would be the case if most of the patients would or could adhere more closely to the prescribed diet.

Cooperation of Patients

It is very difficult to evaluate the degree of cooperation of most patients in regard to the therapeutic regime. Many diabetics fail to follow their diets and then deny to their physicians any break in discipline. In the evaluation of the degree of cooperation we have been helped by routine blood sugar determinations and records of body weight at every consultation.

Table 6 shows the estimated degree of cooperation both as to diet and as to insulin administration. Over one half (53 per cent) of the patients requiring insulin take it strictly as prescribed and 21.4 per cent of them take it very irregularly. A fairly large number of patients in this group belong to the lowest economic level of our society and are unable to obtain any insulin except through government or private charitable institutions.

As far as the diet is concerned, it is noteworthy that the highest percentage (56.6 per cent) of cooperating patients was found in the group treated with diet alone,

while those requiring insulin show the highest percentage of non-cooperators. Among the latter, the chief trouble is not so much in relation to carbohydrate as total caloric intake. Like the obese, nondiabetic as well as diabetic, they are unwilling or unable to resist temptation.

Presenting Symptoms

An attempt was made to analyze the symptoms which most frequently led to the discovery of the disease. Table 7 shows the result of such analysis. The cardinal symptoms, polyuria, polydipsia, loss of weight, and polyphagia, appeared in 44.4 to 86.9 per cent of cases. The most noteworthy fact is the relatively high incidence of vulvitis as a presenting symptom in 23.3 per cent of women. In 12 of the 79 cases with this symptom, it was the only complaint leading to the correct diagnosis.

Complications

We have classified the complications of diabetes in our cases in different categories. Table 8 shows complications directly related to diabetes. Among these, again diabetic vulvitis ranks high, being the most common. Acidosis occurred in 55 cases, in 24 of which coma developed. This is 7.8 per cent of the whole series, a rather high incidence which can be explained by the low educational and economic level of approximately two thirds of our patients. The low reported incidence of retinopathy, 16 cases, is probably explained by two main factors: incompleteness or lack of follow up in the older patients, and the relatively short duration of the disease in the majority of the patients. (The average duration of diabetes for the whole series is 4.6 years.)

Table 9 shows the incidence of conditions which are found more commonly among diabetic than nondiabetic individuals. There is nothing unusual about the number of arteriosclerotics and hypertensives or even the total number of pyogenic infections of the skin and subcutaneous tissues, but the incidence of urinary tract infections is rather low, even if only the severe ones are included.

The low incidence of tuberculosis deserves special attention. It is true that all three hospitals from which our data have been compiled are general hospitals where known cases of tuberculosis are not admitted, but even so, the rate is unusually low especially in a country where the morbidity rate is very high and the mortality rate is 128.9 per 100,000 population[3], second only to diarrhea and enteritis in infants among the leading causes of death. Why the incidence was so low in our series is difficult to explain. Possibly the relatively short average period of observation, the predominance of patients over 40 (when the tuberculosis rate for the general population begins to decline,) and the absence of a mass screening process for tuberculosis in our institutions are contributing factors. On the other hand, of 1334 consecutive admissions to a local tuberculosis hospital during the past seven years, only eight were diabetics. In six of these, the diabetes preceded the onset of tuberculosis; in one, both conditions were diagnosed at the same time; and in the other one, tuberculosis existed prior to the discovery of diabetes.[4] Undoubtedly, more cases will develop among our patients in the near future. Already two of our young diabetics have developed tuberculosis since this study was started.

Deaths

Because of the lack of adequate follow up in about one-third of our cases the number of deaths known to have occurred among these patients is very small. The details are shown in Table 10. Of 31 total known deaths only six can directly be attributed to diabetes and one to an error in treatment (or, rather, ignorance on the part of the relatives of the patient who died in hypoglycemia). In 12 cases, death was due to degenerative vascular diseases, and in 5 to cancer. The 7 other deaths were due to a variety of apparently unrelated diseases.

SUMMARY

An analysis of the characteristics of 700 diabetics in Puerto Rico shows that the findings agree in general with those obtained from similar studies made elsewhere and reported in the literature.

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SEE FOLLOWING PAGES FOR ACCOMPANYING TABLES

TABLE 1 SEX INCIDENCE OF DIABETES IN PUERTO RICO

Sex	Private cases	Charity cases	Total
Males	97 (41.1%)	137 (29.2%)	234 (33.3%)
Females	138 (58.9%)	328 (70.8%)	466 (66.7%)

TABLE 2 INCIDENCE OF DIABETES ACCORDING TO AGE OF ONSET BY DECADES

	Age Decades—Per cent								
Author	1	2	3	4	5	6	7	8	9
Compiled from the literature									
Frerichs	1.0	7.0	10.0	18.0	25.0	26.0	11.0	1.0	
Seegan	0.5	3.0	16.0	16.0	24.0	30.0	10.0	0.5	
Grube		1.7	2.8	11.2	23.1	39.5	18.1	3.4	
Schmitz	0.83	4.11	9.3	17.3	22.3	32.6	10.0	3.3	
Pavy	0.58	4.19	7.13	16.4	24.9	30.7	13.4	2.5	
Kulz	1.0	3.0	4.6	17.2	36.0	26.8	9.2	0.1	
Von Noorden	1.43	1.43	4.2	9.87	16.7	14.3	3.0	0.4	
John	4.5	4.16	6.14	11.8	23.28	26.67	23.45*		
Joslin (9853 cases)	4.7	6.8	7.82	12.29	23.14	27.32	18.0*		
Paniagua and Vizcarrondo	1.8	1.9	4.4	15.0	28.9	29.5	15.7	2.3	0.3

*7th, 8th and 9th decades

TABLE 3 MODE OF ONSET OF DIABETES

		Under 30	Over 30
Rapid	134 (27.7%)	22 (53.6%)	112 (20.3%)
	350 (72.3%)	19 (46.4%)	331 (74.7%)
Gradual	484	41	443
Undetermined	216	13	203
	700	54	646

TABLE 4

Nutritional Status	Mild	Moderately Severe	Severe	Undetermined	Total
Onset under 30 Years					
Underweight	0	2	15	1	18
Normal	6	4	10	1	21
Overweight	7	2	1	0	10
Undetermined	0	1	2	2	5
	13	9	28	4	54
Onset at 30 Years or Over					
Underweight	19	14	10	9	52
Normal	75	26	11	18	130
Overweight	240	62	20	70	392
Undetermined	20	6	2	44	72
	354	108	43	141	646
Total	367(66.1)	117(21.0)	71(12.9)	145	700

TABLE 5 DEGREE OF CONTROL

Good	291	(45.6%)
Fair	207	(32.5%)
Poor	139	(21.9%)
	637	
Undetermined	63	
	700	

Treatment Necessary

Diet Alone	242	(35.8%)
Diet and Insulin 40 Units or less	327	(48.2%)
Diet and Insulin over 40 Units	108	(16.0%)
	677	
Undetermined	23	
	700	

TABLE 6 DEGREE OF COOPERATION

1. Cooperation regarding diet among patients using insulin

Good	84	(27.6%)
Fair	84	(27.9%)
Poor	134	(44.5%)
	302	
Undetermined	133	
	435	

2. Cooperation regarding diet among patients not requiring insulin

Good	97	(56.6%)
Fair	48	(27.7%)
Poor	27	(15.7%)
	172	
Undetermined	70	
	242	

3. Cooperation regarding insulin

Good	142	(53.5%)
Fair	68	(25.6%)
Poor	57	(21.4%)
	267	
Undetermined	168	
	435	

TABLE 7 PRESENTING SYMPTOMS

	No.	Per Cent
Polyuria	446	86.9
Polydipsia	391	76.2
Loss of Weight	258	50.2
Polyphagia	227	44.4
Vulvitis	79	23.3*
Loss of Vision	53	10.3
Pruritus	43	8.4
Neuropathy	27	5.2
Furunculosis	6	1.1
Coma	4	0.7

*23.3% of 339 females in whom symptoms could be ascertained.

TABLE 8 DIABETIC COMPLICATIONS

Vulvitis	79	Intercapillary glomerulosclerosis	19
Acidosis (coma-24)	55	Retinopathy	16
Neuropathy	44	Necrobrosis lipoidica diabeticorum	1
Gangrene	21		

TABLE 9 CONDITIONS FOUND WITH GREATER FREQUENCY AMONG DIABETICS

Arteriosclerosis (general)	155
Coronary	5
Hypertension	138
Cerebral Vascular Accidents	3
Cataracts	58
Pyogenic infections of skin and subcutaneous tissues	78
Urinary tract infections	25
Tuberculosis—Pulmonary	12
Renal	1
Other Infectious diseases	15
Ulcers	11
Pneumonia	7
Idiopathic Hepatomegaly	7
Osteomyelitis	6
Hyperthyroidism	6

TABLE 10 KNOWN DEATHS AND CAUSES

Malignant Neoplasm	6
Coma	4
Cerebral vascular accidents	4
Acidosis	2
Uremia	2
Cardiac failure	2
Coronary occlusion	2
Hepatic insufficiency	1
Acute nephritis (mercury poisoning)	1
Bronchial obstruction (moniliasis)	1
Lobar pneumonia with agranulocytosis	1
Septicemia due to thrombophlebitis	1
Pulmonary embolism	1
Cirrhosis	1
Venous mesenteric thrombosis	1
Tuberculous peritonitis	1
Hypoglycemia	1

SCREENING FOR HIDDEN DISEASE

Screening as a routine function of practicing physicians represents a departure in activities to which the profession as a whole has not completely oriented itself. The reasons for this failure of orientation are numerous and must be given due consideration before attempting to evaluate the likelihood of success in assigning to physicians an additional responsibility of such magnitude. Perhaps the foremost reason for inertia is the traditional role of the physician as healer and therapist. For centuries the public has looked to the medical profession for the cure of diseases and the relief of suffering, to tax-supported agencies for sanitation and preventive medicine. The search for diseases in their earliest stages is an extension of preventive medicine toward medical practice, or an extension of medical practice toward preventive medicine—dependent upon viewpoint. It represents a new form of activity which might be termed "diagnostic preventive medicine," "preventive diagnosis," or "presymptomatic medicine." The field of presymptomatic medicine has not been sharply delineated as a practical challenge for physicians.

Economic factors have presented a constant deterrent to the widespread adoption of presymptomatic diagnosis. It is well known by lawyers, plumbers, garage mechanics and other purveyors of personal services that the public is more ready to make an economic sacrifice to get out of trouble than to stay out. In medicine this vagary of human nature is demonstrated by the rather adequate remuneration for a routine appendectomy as compared with that for a diagnostic survey which certainly takes longer and probably demands at least an equal degree of professional ability. As the medical profession takes on more and more preventive duties it enters fields which are progressively more difficult to finance.

Another deterrent has been the low yield of pathologic findings on the routine use of such diagnostic procedures as the chest x-ray or Papanicolaou's smear. Even cancer detection clinics have been very costly in terms of the number of cases recognized.

Then, too, physicians are primarily interested in testing their wits against problems which are already established. As a group they like to see fullblown diseases rather than apprehensive people who are fortunate enough to be free from them . . .

In spite of these factors which make for conservatism on the part of the medical profession in taking on responsibilities of a preventive nature, presymptomatic diagnosis has been accepted in military, industrial and insurance medicine for many years, and it has made up a large part of the routine practice of pediatricians . . .

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PNEUMATURIA

Report of a Case in a Diabetic With Review of the Literature

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The passage by the urethra of urine containing gas or air is known as pneumaturia. Senator,[1] in 1891, suggested a classification of this condition into three groups, as follows: 1, pneumaturia resulting from air introduced into the bladder by means of instrumentation or catheterization; 2, pneumaturia resulting from gas entering the bladder by way of a fistulous connection, e.g. vesicovaginal fistula; and 3, pneumaturia resulting from gas produced by decomposition or fermentation of urine in the bladder. Group 3 may be further subdivided into the cases with and without glycosuria. This paper is concerned with cases falling into the category of the third group, with special emphasis on the association with glycosuria.

We have reviewed the literature since the first report in 1860 and have collected 20 cases of the primary type of pneumaturia with glycosuria (Table 1), and 19 without glycosuria (Table 2). In five of the cases with glycosuria, the diagnosis of true diabetes is uncertain. In one of these, pneumaturia and glycosuria observed during a state of coma later disappeared.[2] In another case, there was only a past history of glycosuria prior to the onset of pneumaturia.[3] In the remaining three cases,[4,5] glycosuria was not present at the onset of the pneumaturia, but glucose was later found in the urine intermittently. As for the nonglycosuric cases, two of the four patients described by Adrian and Hamm[6] may have had vesico-enteric fistulae secondary to carcinoma, although definite information was not given.

The first mention of what is today considered pneumaturia was in the "Curiosities of Nature," published in 1671.[7] A man was reported to have passed wind by the urethra with or without the passage of urine. Ribes,[8] when prosector to the Medical School of Paris, showed his students an infant whose only malady was the passage of gas by way of the penis. The urine was found to be normal. Celui de Poirry[9] in 1820 stated that the bladder can contain air under certain circumstances.

It was Boismont,[10] however, who in 1825 was the first to mention the spontaneous production of gas in the urinary bladder. Roche[11] in 1836 reaffirmed this. Chomel[12] added the suggestion that the gas may be due to fermentation.

Up to 1860 all the cases reported were instances of fistulous communication between the bowel and the bladder. In that year Raciborski[13] described in detail the first case in which no fistulous connection between the bladder and any other organ was found. He named the condition pneumo-uria, because his patient had developed the gas spontaneously in the bladder. The gas was odorless, but Raciborski had seen some cases in which the gas had the odor of hydrogen sulfide.

Keyes[14] in 1882 reported the first cases in the American literature. They were the result of instrumentation in two men with prostatic hypertrophy. Guiard[15] first pointed out the occurrence of pneumaturia in diabetes in 1883 and reported four cases. A series of case reports appeared since then.[16-36]

Mueller[18] reported the first analysis of the gas found in diabetic pneumaturia; it contained a predominence

TABLE 1 GLYCOSURIC CASES REPORTED IN THE LITERATURE

Author	Year	Age and Sex	Organism	Pathology
Guiard	1883	77 M	?	Bladder stone
		60 M	?	Cystitis; suppurative pyelonephritis
		51 M	?	Bladder stone
		60 M	?	Enlarged prostate
Dumenil	1883	45 M	?	Urethral stricture
Thomas	1885	old M	?	Cystitis
Ralfe	1887	middle aged F	?	Cysto-pyelonephritis
Senator	1891	66 M	Yeast	Prostatic hypertrophy
Mueller	1892	60 M	B. coli	Prostatic hypertrophy; cystitis
Frisch	1896	64 M	B. coli; yeast	Cystitis
Pere	1897	38 M	B. coli	Cystitis
Von Loghem	1905	65 M	Proteus vulgaris	Prostatic hypertrophy
Eve	1909	middle aged M	B. coli	Cystitis; ascending pyelonephritis
Sorensen	1910	60 M	B. lactis aerogenes	Prostatic hypertrophy; cystitis
		64 M	B. coli	Urethral stricture
Mullern-Aspegren	1921	73 M	Saccharomyces	Prostatic hypertrophy
Young	1922	76 F	B. coli; yeast	Urethral stricture; cystitis; diverticulum of bladder
Walthard	1922	66 M	B. coli; B. lactis aerogenes	Cystitis; hypertrophy of prostate
Riley and Bragdon	1937	52 M	Yeast	Urinary retention; cystitis
Arthur and Johnson	1948	56 F	B. coli; fungus	Diverticulum of bladder; cystitis
Spring and Hymes	1952	31 F	B. coli	Cystitis

TABLE 2 NON-GLYCOSURIC CASES REPORTED IN THE LITERATURE

Author	Year	Age and Sex	Organism	Pathology
Raciborski	1860	40 M	?	Not available
Keyes	1882	67 M	?	Prostatic hypertrophy
		68 M	?	Probable urinary fistula*
Tisne	1887	77 M	?	Prostatic hypertrophy
Favre	1888	? F	B. coli	Cysto-pyelonephritis
Schow	1892	? ?	?	Cord bladder
Heyse	1893	35 F	B. lactis aerogenes	Cord bladder
Schnitzler	1894	46 F	B. lactis aerogenes	Cystitis
Kelly and MacCallum	1898	36 F	?	Renal calculi
Bacari	1899	38 F	B. coli; Staph aureus	Cystitis
Wildbolz	1901	52 M	B. lactis aerogenes	Urethral stricture
Taussig	1907	34 F	B. coli	Cystitis
Adrian and Hamm†	1907	35 F 27 M	B. coli B. coli	Cystitis Urethral stricture
Cealic and Ceocalteau	1914	32 F	B. coli	Urethral stricture cystitis
Thevenot and Leboeuf	1923	53 M	B. Friedlander	Cystitis
Mulsow and Gillies	1934	53 M	Nocardia; strep. and staph.	Cystitis; prostatic hypertrophy

*This case is probably one of vesico-enteral fistula and perhaps should have been excluded. A postmortem was not done to confirm this.

†Reported four cases, but two were probably malignancies with vesico-enteral fistulae, and so are omitted.

Note: Some of the early reported cases of cystitis, bladder stone, and cysto-pyleonephritis were probably secondary to an obstructive uropathy.

of hydrogen. Favre[24] in 1888 isolated a gas-forming bacterium at autopsy from a nondiabetic woman with cystitis and pyelonephritis. Gas was present in the bladder and ureters. Senator[1] first reported the association of pneumaturia with cystitis in a patient who was a diabetic. In his patient the urine was acid and had the odor of a fermented yeast mixture. The gas was largely carbon dioxide and the fermented urine contained considerable alcohol on distillation. Yeast cells were found in the urine. Frisch's patient, a diabetic male 38 years old, had pneumaturia caused by a yeast cystitis.[19]

Kelly and MacCallum[25] in 1898 reviewed all the reported cases of pneumaturia and added one of their own. Nine out of the 16 had glycosuria. Obstruction to the lower urinary tract was present in the majority. Two had vesical paralysis following myelitis.

Eve[3] stated that pneumaturia in a glucose-free urine may indicate a masked glycosuria. His patient had glycosuria before the onset of pneumaturia, but not during or after its disappearance. The cases of Sorensen[4] and Walthard[5] confirmed this observation. Their patients were aglycosuric at the onset of pneumaturia and later became glycosuric. In Walthard's patient the gas produced seemed to be less after glycosuria was found.

Arthur and Johnson[30] collected all the cases of pneumaturia in the American literature. There were seven, including their own. Of these, three were in diabetics who had a complicating cystitis. We wish to report the eighth case, and the fourth in a diabetic with a complicating cystitis.

CASE REPORT

A 31-year-old woman with a history of diabetes mellitus of 12 years' duration came to the office of one of us (M.S.) on April 21, 1951. For three years she had been troubled with swelling of the feet of varying degree. She was taking 30 units of protamine zinc daily, but did not follow a diet. She had had poor vision for the past two to three years because of bilateral cataracts. Two brothers had diabetes.

The physical examination was normal except for slight hypertension, cataracts and very slight edema of the legs. The blood pressure was 160/90. The neurological examination was within normal limits. The fasting blood sugar was 205. The urine contained sugar graded 4 plus, and the albumin graded 1 plus.

The patient was advised to take ammonium chloride and a low salt diet. She was advised to take 50 units of NPH insulin daily. Her initial complaint disappeared in a few weeks. She was seen again on Sept. 22, 1951 for a check-up and minor complaints. No leg edema was present.

She was seen again two weeks later. Although improved, she complained of a bearing-down feeling at the end of urination and felt as though urination was incomplete. The urine contained sugar graded 4 plus, albumin graded 2 plus; many white blood cells and red blood cells were found on microscopic examination. Because of the suspicion of the presence of an early neurogenic bladder related to the diabetes, she was referred to one of us (J.H.) for urologic study.

In the course of the urologic examination on October 10, 1951, the patient volunteered the information that once daily during the past month, usually after work, she passed gas via the urethra at the end of urination. The gas was passed in an explosive manner and with a feeling of a bubbling sensation in the urethra.

A roentgenogram taken before cystoscopy showed the presence of gas in the bladder. The bladder contained 40 cc. of hazy residual urine. On cystocopy, the bladder mucosa and trigone were seen to be reddened throughout. The bladder neck was red and edematous. The ureteral orifices were both normal. The patient felt the first urge to void when the bladder contained about 200 cc. of water and had marked urgency at about 300 cc. This was indicative of a mild hypertonic bladder associated with cystitis. No gas bubbles were seen being emitted from the ureteral openings. Catheters were passed to the pelvis of each kidney. Urine flow and split function indigo-carmine tests were normal. The urine was grossly clear from each kidney. A retrograde pyelogram was within normal limits.

The bladder urine showed the presence of albumin graded 1 plus, and 2 per cent sugar. The microscopic examination showed numerous white blood cells and about 15 red blood cells per high power field. The sugar had disappeared from the bladder and kidney urine specimens after they had stood overnight.

The culture of urine from the bladder revealed escherichia coli in abundance (Dr. A. J. Weil). This strain showed gas formation from dextrose and lactose well above average. The culture of urine from the left kidney showed escherichia coli with the same cultural behavior. From the urine of the right kidney a few colonies of bacillus alcaligenes faecalis were cultured. This organism is not a producer of gas from carbohydrates; the significance of its presence is difficult to assess. Accidental contamination could not be excluded from the single examination. Antibiotics sensitivity tests of the organisms isolated from the urine of the bladder showed no sensitivity towards penicillin and bacitracin, a high degree of sensitivity towards aureomycin, chloromycetin, and terramycin, and sensitivity in high concentration only towards streptomycin and dihydrostreptomycin.

On October 14, 1951, in order to evaluate further her urologic status, the patient was seen again by one of us (J.H.). Cystoscopy after the patient had voided urine which appeared clear on inspection revealed the absence of residual urine. The bladder capacity and tone were normal. The mucosa was approximately normal in color; the trigone was moderately injected. The ureteral orifices were normal. Some edema of the bladder neck was noted. The urine was sugar free, and all the other tests were normal.

Starting October 18, 1951, the patient was given aureomycin, later followed by chloromycetin. The day after the institution of therapy, the pneumaturia disappeared completely. By the third day of treatment, urinary frequency had also disappeared. A relapse occurred two weeks after the therapy was discontinued. On November 24, 1951, she was given Gantrisin, followed by Mandelamine. The pneumaturia disappeared in 72 hours. She has remained symptom-free for two months. The examination of the urine for pus and blood cells has been negative.

COMMENT

A woman with diabetes and with a history of cystitis developed pneumaturia. An inflamed bladder on cystoscopy and gas in the bladder on roentgenogram confirmed the diagnosis. There was no history of prior instrumentation or abnormality of the urinary tract. Studies revealed the presence of escherichia coli in the urine of the bladder and left kidney, with the complete disappearance of sugar in these specimens when they were allowed to stand overnight. The organism was found to be a fermenter of dextrose and lactose. It was sensitive to aureomycin, chloromycetin and terramycin.

In view of the presence of 40 cc. of residual urine on the first examination the possibility of an early diabetic cord bladder was considered as the origin of the cystitis. However, the presence of about normal bladder capacity and the first desire to void at about 200 cc. (250 cc. is normal), ruled out a cord bladder. We believe the small amount of residual urine found on the first examination was due to the presence of cystitis and edema of the bladder neck. (The gas may be produced in the bladder or kidneys. In our case, the gas was produced in the bladder, as shown on roentgenogram.) Residual urine in the bladder enabled the infecting organism to act on the glycosuric urine for long periods of time and thus produce gas; however, residual urine is not necessary for gas production. In our case, the pneumaturia continued even after the disappearance of the residual urine from the bladder.

The pneumaturia disappeared within 48 hours after institution of aureomycin therapy, but recurred within two weeks after the discontinuation of the therapy, probably because the aureomycin was not administered for a long enough period. Two days after the institution of Gantrisin, followed by Mandelamine, she became asymptomatic. At present, January 14, 1952, the patient is free of pneumaturia and associated urinary symptoms.

DISCUSSION

The presence of residual urine offers a favorable medium for the growth of bacterial and saccharomycelial organisms. The gas is usually produced in the bladder. In the kidney, unless obstruction with stasis is present, gas formation will not occur, as the urine passes down very rapidly from the kidneys to the bladder.

Analysis of the reported pneumaturia cases, and our own, shows that: 1, it occurs with about the same frequency in glycosuric and nonglycosuric patients; 2, since only 39 cases have been reported in the literature, it probably occurs more frequently than has been reported; 3, the urine is usually acid, but neutral or ammoniacal when decomposition sets in; 4, escherichia coli, B. lactis aerogenes and yeast are the most frequent organisms found on urine culture; and 5, the gas produced is usually odorless.

On analysis Mueller[18] found the gas in diabetic urine to consist of carbon dioxide, 9.1 per cent; hydrogen, 57.3 per cent; nitrogen, 33.5 per cent; and methane, 0.79 per cent. As the urine stands, more carbon dioxide is formed, up to 19 per cent, and hydrogen decreases in amount as a result of the fermentation. Hydrogen forms the main bulk of the gas in diabetics. In nondiabetics the gas formed is mainly carbon dioxide.

The gas produced in glycosuric cases is due to fermentation with production of butyric and lactic acid. Distillation of the urine may yield considerable amounts of alcohol. As stated before, the presence of residual urine and glycosuria offers a favorable medium for the growth of organisms.

The gas produced in those cases without glycosuria is believed to be due either to proteolytic breakdown of a special kind of albumin which is present in the urine, or to an escherichia coli strain which can form gas from the breakdown of normal albumin. The larger part of the gas formed in these instances consists of carbon dioxide. Another theory for the formation of gas in nonglycosuric urine was postulated by Mulsow and Gillies,[36] who stated that the acid urine from the kidneys acting upon bicarbonates in retained bladder urine may produce gas. Lastly, it may be caused by some non-reducing carbohydrate; by glucose in amounts too small to be detected by methods in use; by glucose that occurs only at intervals; or by glucose that may have been previously fermented out (Sorensen[4]). In view of the latter facts, every case of pneumaturia should be carefully studied for the presence of diabetes, even in the absence of sugar in the urine.

Pneumaturia does not result from ordinary ammoniacal fermentation of the urine or from putrefactive decomposition, because the hydrogen sulfide gas that is formed is soluble. Symptoms are not striking. There may be frequency because of the associated cystitis and the distention of the bladder with gas. The passage of gas causes no pain, but a tickling sensation, and usually occurs at the end of urination in an explosive manner. The urine is cloudy and may contain pus. Recovery is rapid with the use of the appropriate drugs or antibiotics, control of the diabetes, and the elimination of the residual urine, if present. Death is due to infection of other organs, e.g. pyelonephritis with uremia. The

incidence of pneumaturia must be much greater than the reported number of cases. This may be due to the fact that either it is not recognized or not reported. In our case, the patient mentioned incidentally that she had been passing gas for one month. The fact that we were cognizant of this condition enabled us to recognize and eliminate it.

SUMMARY

A case of pneumaturia in a diabetic woman, with cystitis, due to an infection with escherichia coli, has been reported with a review of the literature.

Pneumaturia in itself is unimportant. It is significant as part of a symptom complex usually associated with urinary obstruction and infection, with or without diabetes. Antibiotics will not clear up the pneumaturia and the underlying infection unless the obstruction, if present, is eliminated and the diabetes controlled. A urine that is persistently negative for sugar in the presence of pneumaturia does not necessarily exclude diabetes, as the sugar may have been completely fermented by the infecting organism.

ACKNOWLEDGMENTS

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The Effects Of Stressful Life Situations On The Concentration of Blood Glucose In Diabetic and Nondiabetic Humans*

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The blood glucose concentration is the resultant of a dynamic equilibrium between the amount of glucose taken up by the tissues and that supplied to the blood by the liver. Under ordinary circumstances this concentration is maintained with relative constancy in the healthy individual, but fluctuates much more widely in the person with diabetes mellitus. In all individuals the ingestion of carbohydrate food tends to raise the blood glucose level, and physical exercise tends to depress it. The administration of the hormones which are concerned with the regulation of carbohydrate metabolism (such as epinephrine, insulin, adrenal cortical steroids, and pituitary growth hormone) may also cause changes in the circulating glucose. Physical stresses such as infections and trauma likewise affect the blood glucose regulation, apparently because they lead to the elaboration of these hormones as a part of the adaptive processes of the organism. The function of the endocrine glands which regulate carbohydrate metabolism may be altered also by stimuli arising in the external environment in the form of events or situations which are evaluated by the individual as threatening, and which therefore initiate adaptive responses mediated through the central nervous system. It has long been felt that stimuli of this sort might also lead to changes in the level of circulating glucose, and in fact experimental evidence has indicated that hyperglycemia can be produced in diabetic persons during psychiatric interviews.[1]

The present study was undertaken in order to examine the effects of stressful events and situations upon the level of glucose in the circulating blood of diabetic and nondiabetic individuals.

*From the Department of Medicine, Cornell University Medical School. The authors are indebted to Dr. Edward Tolstoi for his encouragement and criticism of this work. Read at the meeting of the American Diabetes Association, Chicago, June 7, 1952.

METHODS

The chemical, physical, and psychological procedures utilized in these studies have been outlined extensively in other publications.[2, 3, 4] The short term laboratory studies described herein were performed on individuals who were in a resting, post-absorptive state. During the procedures there were no changes in physical activity, and no drugs, food or fluids were administered which might affect the glucose level. Stress and control studies were performed at the same time of the day in order to avoid errors introduced by diurnal fluctuations in blood glucose and urine output. Insofar as possible, individuals were used as their own controls in later experiments. Diabetic persons who had been receiving insulin received their last injection 24 hours before the beginning of the study.

Stresses were introduced in these experiments by the discussion and reenactment of events and situations which were known to be of great significance to the subjects, whose past history and present life situation had been studied prior to the experimental procedure.[3, 5] After an initial hour of waiting in a neutral setting, the stressful situation was abruptly introduced during the second hour of interview. After this hour an attempt was made to remove the stress and restore the subject to his former state of tranquility. Psychological observations were made on the subjects before, during and after the procedure, and equally careful observations were made during the control procedures.[2]

Methods for determination of blood glucose utilized in this study respond to so called "true" glucose levels and largely exclude reducing substances other than glucose. In earlier studies the precipitation method of Herbert and Bourne[6] was utilized, and one of Benedict's reagents was used in the color reaction.[7,8,9] In later studies Folin's precipitation method for unlaked blood was utilized.[10] These two methods were compared with each other and with the Somogyi method[11] and were found to yield results within 2 to 5 mg. per 100 cc. of each other at levels below 100 mg. per 100 cc.

RESULTS

Nondiabetic Individuals:

In post-absorptive nondiabetic individuals the "true" glucose concentration in venous blood was found to lie between 50 and 80 mg. per 100 cc. On a morning after an overnight fast this level was found to fall gradually toward the lower value. In the resting individual who is in a relatively serene state with regard to his environment, the blood glucose was found to be relatively stable, although fluctuations of the order of 2 to 3 mg. appeared to occur in samples taken at frequent intervals. These fluctuations approach the magnitude of the inherent error in blood glucose methods, but they may also represent some actual fluctuation in the level itself. As fasting continued the blood glucose concentration fell slowly toward a minimum level which varied for each individual, but in general lay between 40 and 55 mg. per 100 cc. Such a level was often attained by 11 a.m. or noon. At this point the glucose ceased to fall and remained steady, or even rose somewhat. At about this time the concentration of circulating ketone bodies began to rise from the normal level of 0.2 to 1.5 mg. per 100 cc. These changes were accompanied by a fall in the circulating eosinophiles and often also by a slight increase in the rate of excretion of water and electrolytes.[4,3] It has been felt that these metabolic changes represent a part of the adaptive response to fasting.

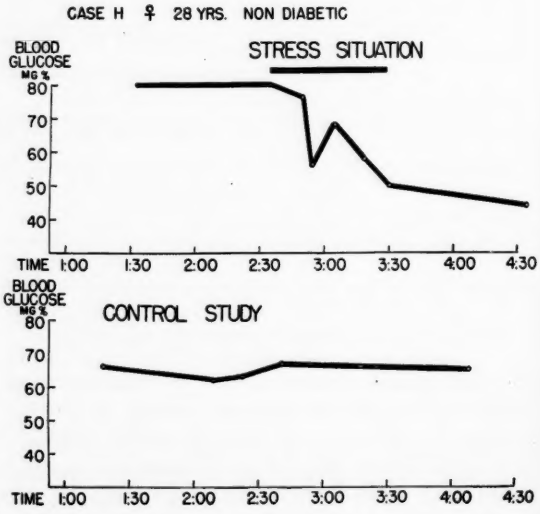

FIGURE 1 Fall in blood glucose occurring in a 27 year old nondiabetic woman in a stress situation. Similar changes did not occur in the control study. (Below)

In individuals exposed to stressful situations it was found that the usual response was a fall in the blood glucose. In nondiabetic persons the magnitude of this fall was from 5 to 20. In part the size of the fall was dependent upon the initial level of blood glucose. Those individuals in whom the blood glucose was at a low level (50-60) at the beginning of the experiment developed a much smaller depression under stress than did those in whom the initial level was higher (70-80). An example of a fall in blood glucose

occurring during stress is illustrated in Figure 2. After an hour of peaceful waiting this 28 year old woman was suddenly engaged in a discussion of the fact that during the war she had had a love affair while her husband was overseas, which had resulted in an illegitimate pregnancy and a criminal abortion. Although her husband was unaware of this affair, her mother had found out about it and was using the knowledge as a means to dominate her daughter. The interview aroused in the subject mixed feelings of anxiety, guilt, and resentment, and was associated with various bodily changes such as tachycardia, sweating and crying. It was observed that during the procedure the blood glucose fluctuated rapidly, and fell from an initial level of 80 to a final level of 44. Despite the interviewer's reassurance during the last hour, the blood glucose did not return to its former level. The fall in glucose was accompanied by a rise in ketonemia and diuresis similar to that seen during the adaptation of fasting. Such changes in the blood glucose level did not occur in the control study.

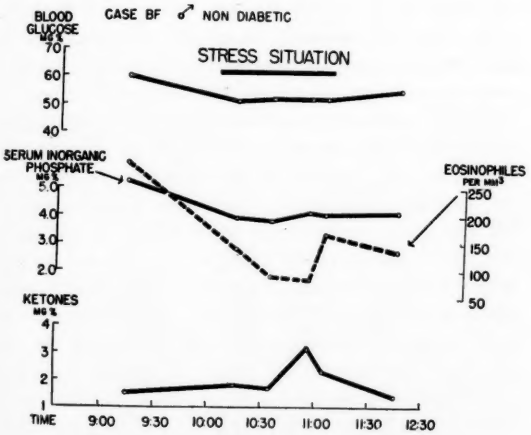

FIGURE 2 Fall in blood glucose, fall in circulating eosinophiles, fall in serum inorganic phosphate and rise in blood ketones, occurring in a nondiabetic individual in a setting of stress.

In further studies it was found that when the blood glucose falls during stress, this fall is often accompanied by a fall in circulating eosinophiles and also by a fall in serum inorganic phosphate (Figure 2). It was also found that these and similar reactions to stress situations may be accompanied by a fall in the circulating protein bound iodine, followed by a rise (Figure 3). These observations, considered together with the fact that in settings of stress, subjects often develop tachycardia, sweating and muscle tension, suggest that the fall in glucose may be in part a result of an increase in the uptake of glucose by the tissues, and that in turn may be secondary to an overall increase in metabolism of the subject. In the diabetic the metabolic rate is elevated during ketosis.[12]

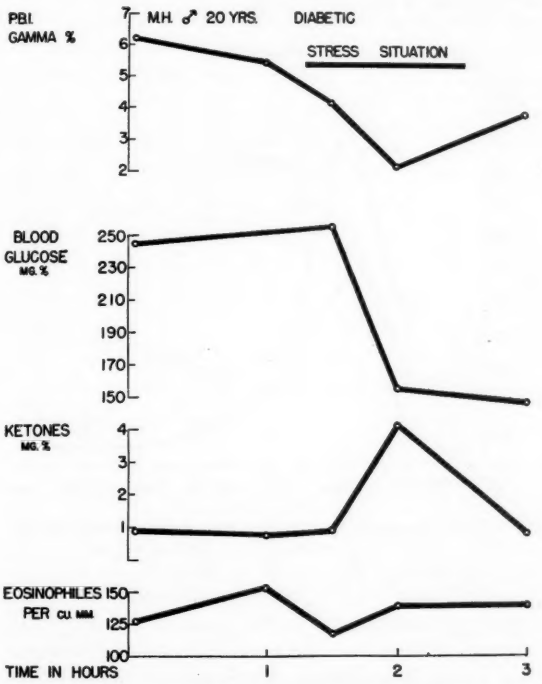

FIGURE 3 Fall in serum protein-bound iodine accompanying fall in blood ketones in response to stress. After such a fall the PBI usually rises to a level higher than the initial level.

A rise in the blood glucose was rarely encountered in nondiabetic persons in response to the stress situations which arose during these studies. Most of these stress situations evoked reactions of anxiety, resentment, or dejection. Overwhelming reactions of panic, fear, or intense rage, which might be expected to be associated with the elaboration of epinephrine, and the mobilization of liver glycogen, rarely developed during our observations on nondiabetic individuals.

It was found that the response to ingested glucose might also be altered during adaptation to stressful life situations. Standard intravenous glucose tolerance curves[13] performed in a setting of stress which evoked a reaction of anxiety and tension in the subject, led to a "flatter" glucose tolerance curve than those seen during

periods of relative relaxation and serenity (Figure 4). On the other hand, in other individuals intravenous glucose tolerance curves performed during stress situations evoking feelings of sadness, resentment, and loneliness, were sometimes higher than those observed in the same persons during periods of relaxation and serenity. The theoretical explanation for these two types of response is discussed below.

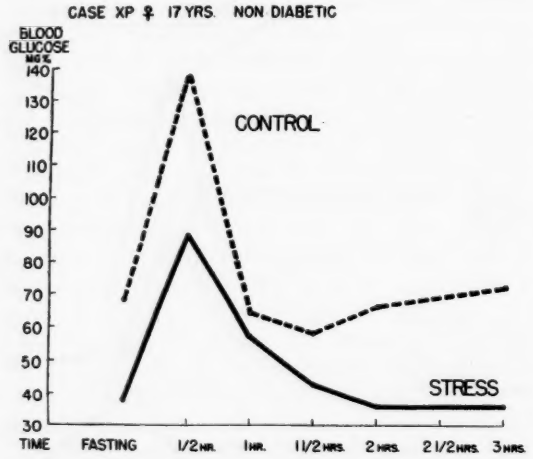

FIGURE 4 Changes in the standard intravenous tolerance curves, occurring in response to a stress situation.

In individuals who received no glucose, the diuresis which accompanied the reaction to stress was sometimes accompanied by the appearance of traces of glucose in the urine. Two instances of this were observed in individuals with low and falling levels of blood glucose, suggesting that so called "emotional glycosuria" is not dependent upon the development of hyperglycemia.

Diabetic Individuals:

In diabetic individuals in a control situation of rest and serenity it was found that at high levels the blood glucose concentration sometimes "spontaneously" fluctuated as much as 10 to 15 mg. within a 15 minute period. However, under such circumstances it was relatively steady throughout a morning, falling gradually as fasting continued. This fall in the face of fasting was greater in magnitude than that seen in the nondiabetic. The phenomenon of "fasting diuresis" appeared in the diabetic as well as in the nondiabetic.[14]

In such control studies it was found that there was very little correlation between the level of glucose in the venous blood of diabetics and the rate at which they excreted water, glucose and ketone bodies.[14] In general, glycosuria was not seen in diabetic persons whose blood glucose was not abnormally elevated, but the occurrence of a "low renal threshold" for glucose was found to be not uncommon. A number of individuals were observed with a heavy glycosuria and a relatively low or even "normal" blood glucose. Although individuals who were excreting water, glucose and electrolytes at an abnormally rapid rate usually had an elevated level of blood glucose, many exceptions to this were observed. It was similarly observed that the relation between the blood glucose and blood ketone concentrations was not parallel.[2] Although diabetic persons with low or normal levels of blood glucose usually had a low or normal level of blood ketones, many instances were observed of persons with a low blood glucose level and a high blood ketone level, or vice versa.

Examples of such observations are illustrated in Figures 5 and 6. In the first control study (Figure 5) the subject's blood glucose fluctuated between the levels of 291 and 271 during a morning of rest and relative serenity. His blood ketone level likewise fluctuated in the range of 1.1 to 1.9 mg. per 100 cc., which is the upper limit of "normal" under the circumstances of these experiments. Despite the fact that his urine glucose concentration was 7.5 per cent, his rate of excretion of water, electrolytes and ketone bodies was within normal limits. The second control study (Figure 6) was performed on a young diabetic man of 21 years on the morning following an altercation with his father. He was under stress during this morning in the sense that his memories of the event were fresh and he was worried about its consequences. However, no additional stress was imposed upon him by the introduction of new stressful situations or the reactivation of the old one, nor was any attempt made to reassure him and ameliorate his unhappiness. Subsequent interviews with him indicated that his feelings had not changed much throughout this morning, although he became somewhat more cheerful toward its end. It was observed that he was in a moderately severe state of ketosis at the beginning of the observation, with a blood ketone level of 23.8 mg. per 100 cc., and that this level did not change greatly during the observation period. His blood glucose level on the other hand was considerably lower than that of the previous subject (195). He had a marked polyuria and glycosuria. His rate of urine output was 4.2 cc. per minute, his glucose output was 319 mg. per minute, and his ketone output was 1.93 mg. per minute. The concentration of glucose in his urine, however, was essentially the same as that of the other subject.

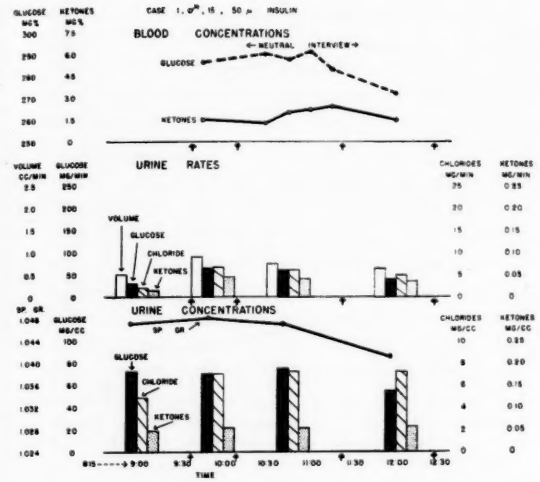

FIGURE 5 Normal rate of excretion of water and electrolytes and "normal" level of blood ketones in an individual with a relatively elevated blood glucose and a 7.5% concentration of glucose in the urine, in the absence of stress.

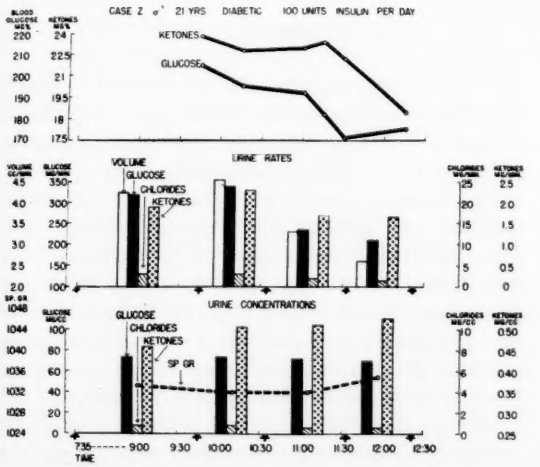

FIGURE 6 Polyuria and elevated blood ketones occurring in the presence of a less elevated blood glucose level in a diabetic individual throughout a morning in which he was under stress. Urine glucose concentration is the same as that of the subject in Figure 5

When the diabetic individuals were exposed to stressful situations the instability in their blood glucose was often pronounced. Rapid fluctuations occurred, usually superimposed upon a steady fall of much greater magnitude than that seen in nondiabetic persons under stress. This fall was usually accompanied by a rise in blood ketone concentration, and by a diuresis and increase in glycosuria (Figure 7). On some occasions these rapid falls in blood glucose were associated with hypoglycemic symptoms, and levels as low as 27 mg. per 100 cc. of blood glucose were attained; but usually there were no accompanying symptoms of hypoglycemia and the fall in blood glucose was arrested before low or even normal blood glucose levels were approached. As the blood ketones rose, the blood glucose tended to stabilize.

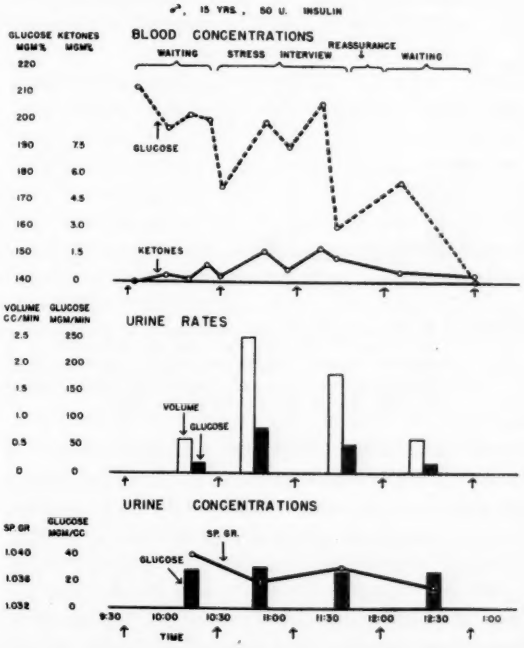

FIGURE 7 Rise in blood ketones, diuresis and increased glycosuria occurring in association with a fall in blood glucose in a diabetic under stress.

In other (less frequent) instances, there was a rise in blood glucose concentration in response to stress. This usually was not associated with any significant change in blood ketone concentration, and was often accompanied by a relative oliguria and decrease in glucose excretion. (Figure 8) Such a rise in blood glucose usually occurred in situations productive of great fear or overwhelming anger, whereas the more common type of stress situations were associated with a fall in blood glucose.

In diabetics acutely exposed to stress situations, the correlation between blood glucose level on the one hand, and blood ketone level, water excretion, and glucose excretion on the other hand, was often more

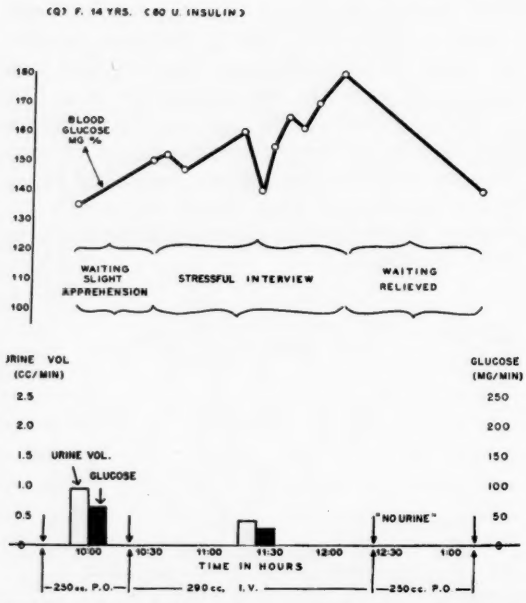

FIGURE 8 A rise in blood glucose occurring in a diabetic in a setting of stress. This rise was accompanied by a relative oliguria despite the high concentration of glucose in the urine and despite the administration of fluids during the period of the study.

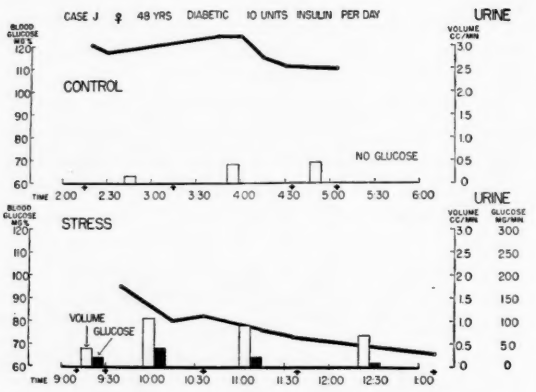

FIGURE 9 Changes in the "renal threshold" for glucose in a diabetic woman in association with her reaction to changing life situations.

inverse than direct. The usual pattern was that of increasing diuresis and glycosuria as the blood glucose fell. However, on some occasions frightened diabetics who developed hyperglycemia were observed to develop glycosuria where they had had none before.[14] Serial studies of individual subjects also indicated that the level of blood glucose at which glucose appeared in their urine changed under stress. The subject of the studies illustrated in Figure 9 had no glucose in her urine at a blood glucose level of 110 to 124 on a day when she was relatively secure and happy; but on a day later when she felt lonely, unloved, angry, and dejected, because her husband had left town to visit his mistress, she had a constant glycosuria at the lower blood glucose level of 95 to 66.

As in the nondiabetic, it was found that in the diabetic also the adaptation to stressful situations might be associated with changes in the shape of the glucose tolerance curve. In general, it appeared that situations associated with reactions of dejection, resentment, and loneliness, were associated with a higher and more prolonged glucose tolerance curve, than that seen in the same individual in a setting of more tranquility and happiness; whereas situations associated with reactions of anxiety and tension might lead to a less elevated curve, sometimes associated with a period of relative hypoglycemia in the third or fourth hour.[8,14] In these respects the diabetic responses were similar to the nondiabetic, although the abnormalities in the curves were much greater.

COMMENT

It is apparent that when humans are exposed to stressful situations, the usual initial effect upon their blood glucose is a transient fall in its concentration. Selye, in his study of the effect of non-specific stress upon laboratory animals, found that in them also the initial response was a fall in blood glucose.[15] Evidence from other animal experiments is in general conformity with this finding.[16,17] This fall occurs apparently because of an increased uptake of glucose by the tissues, which in turn appears to be a part of an overall increase in metabolic activity. Whether or not the glucose output from the liver is also inhibited is not known.

Rarely was an initial increase in blood glucose observed during stress in post-absorptive nondiabetics, and it was not commonly seen in diabetics. In those instances in which it appeared in diabetics it seemed likely that the strong reactions of fear or anger with which it was associated were probably accompanied by an elaboration of epinephrine, and that the hyperglycemia was the result of mobilization of glycogen from the liver. The few instances of rises in blood sugar of 5 to 10 mg. per 100 cc. which were observed in nondiabetics were associated with similar reactions of fear. Among nondiabetics in our studies, however, instances of this type were so few that one cannot draw any conclusion from

them. Mirsky[1] also was unable to demonstrate a hyperglycemia in nondiabetic individuals during stressful interviews. Others have reported that nondiabetic individuals in more prolonged and severe settings of stress (such as aviators prior to hazardous flights,[18] or players during football games[19]) may have a hyperglycemia as great as 180 mg. per 100 cc. or higher. The administration of exogenous epinephrine to nondiabetic individuals often leads to a rise in blood glucose of 50-100 mg. per 100 cc. Such a transient epinephrine hyperglycemia occurring in a setting of "fight or flight" in a fasting individual is uncommon in both diabetics and nondiabetics, and is not evoked in the usual reaction to stress situations. It appears to be an emergency adaptive mechanism, reserved for acute and overwhelming situations.

It has been pointed out elsewhere that the maintenance of the functional integrity of the mammalian organism depends upon the maintenance of a constant supply of glucose to the central nervous system.[21] When the blood glucose concentration falls below a critical level the function of the brain is seriously impaired and homeostatic mechanisms are brought into play to restore the glycemia. In our experience this critical level for most humans lies in the range of 35 to 50 mg. per 100 cc. of true glucose in the venous blood. As fasting proceeds the blood glucose descends slowly toward this level, at which point several metabolic changes take place. The production of ketones by the liver is accelerated, the respiratory quotient falls and the muscular tissues largely cease to utilize glucose, so that the larger proportion of this substance is reserved for the central nervous system. The rise in ketones which occurs at such times is undoubtedly an adaptive mechanism which has the effect of making available a substitute metabolite for the use of the musculature. The evidence suggests that these metabolic adaptations are mediated through the anterior pituitary and the adrenal cortex. The pituitary hormones involved appear to include the growth hormone, the adreno-cortico-tropic hormone and the "RQ depressing factor" recently described by Recant.[22] The effect of ACTH is of course mediated through the so-called "sugar steroids" of the adrenal cortex. The general effect of all these substances is to decrease the uptake of glucose by the muscular tissues and to increase the production of glucose and ketone bodies by the liver. Kinsell has suggested recently that ACTH and the cortical steroids also may have the effect of increasing ketone utilization in the periphery.[23] All of these metabolic changes may be looked upon as "protecting" or "conserving" the available supplies of glucose.

The rapid fall in blood sugar which occurs in humans in response to stress situations likewise initiates an increase in ketonemia. This hyperketonemic response appears to be the adaptive process which commonly occurs in both diabetic and nondiabetic individuals. In diabetics this response may attain such magnitude that when it occurs in conjuction with a "stress diuresis" it may lead to the clinical syndrome which is called ketosis. The emergency epinephrine mechanism in the diabetic has less clinical significance. It temporarily delays the appearance of ketosis, and may lead to hyperglycemia as a result of mobilization of glucose from the liver. This phenomenon is seen sometimes in laboratory animals also, in which a transient elevation of the blood sugar may occur during the initial stages of stress reactions.[15]

When glucose is administered to individuals at a time when they are adapting to stress situations it is apparent that two types of response may occur: The glucose tolerance curve may be either flatter or more elevated than that seen in situations of relative serenity. The reason for this is not entirely clear, but the following explanation seems likely. It has been pointed out that when a *fasting* individual in a relatively serene state is exposed to a stressful situation his blood glucose falls initially, but that as the exposure to stress continues he develops a ketonemic response, and at this time his blood glucose ceases to fall and may actually begin to rise. When an individual in a relatively serene state is given glucose and at the same time is *newly exposed* to a stress situation, his glucose tolerance curve is usually flatter than if he had not been exposed to stress. It may be supposed that the greater uptake of glucose by the tissues, which seems to be the cause of the fall in blood sugar in the fasting individual, causes a flatter curve in the individual to whom glucose is given. If an individual *who has been exposed to stress for some time,* and who has developed a ketonemic response, is then given glucose, his glucose tolerance curve is *higher* and *more prolonged* than it would be in the absence of stress. It is probable that this ketonemic response is associated with a decreased utilization of glucose by the tissues, and that this is the reason why the ingested glucose rises to higher levels in the blood. Acute situations of stress are commonly associated with feelings of anxiety and apprehension, whereas more prolonged situations are commonly associated with feelings of dejection, loneliness, and resentment. This seems to explain why the mood changes and changes of the glucose tolerance curve have a certain parallelism. However, the metabolic changes and the mood changes

do not appear to be causally related, but seem to be simultaneous reactions to stimuli arising in the external environment and evaluated on both a "conscious" and "unconscious" level. The very high levels of blood glucose usually seen in individuals in diabetic coma may be explained by the fact that such individuals often continue to ingest glucose long after the ketonemic response to stress has been established. In individuals who cease to eat during the period in which ketosis is developing, the level of blood sugar may not be so greatly elevated.

In the labile diabetic who is exposed to rapidly changing life situations, the occurrence of rapid changes in the capacity of the patient to utilize glucose appears to account for much of the difficulty in controlling the disease.[3]

The relationship between the urine volume, glycosuria, and the level of blood sugar has been one which has always interested the clinician. It is well known that the excretion of large quantities of glucose in the urine may be associated with an osmotic diuresis and an accompanying loss of water and electrolytes. However, because of the disparity between the disturbance of carbohydrate metabolism and the disturbance of fluid balance which is seen in some patients, there has been a clinical impression that there is a "renal factor" present in diabetics. Recent evidence has indicated that the adrenal cortical hormones affect the ability of the renal tubule to reabsorb glucose and thereby "lower the renal threshold" for these substances.[24] The present studies have provided further indication of the importance of such "renal factors".

The transient diuresis which occurs in the normal individual as he adapts to fasting is not the result of changes in his blood glucose or ketone level. It is a water diuresis of undetermined mechanism, which is often associated with an increased excretion of electrolytes, but also is often accompanied by a fall in the specific gravity of the urine. It may be, as Gamble has suggested, that this water diuresis is "adaptive" in the sense that it gets rid of some excess of body water which appears as the body shifts from glucose to a fat type of metabolism.[25] The diuresis which occurs in a setting of stress is similar to the "fasting" diuresis and possibly arises by the same mechanism. On the few occasions when we have observed so-called "emotional" glycosuria in normal persons in a setting of stress, this glycosuria has appeared in the course of a stress diuresis at a time when the blood glucose was normal or low. This suggests that such a diuresis is associated with hormonal effects upon the renal tubule which tend to depress the reabsorption of glucose; for to explain this phenomenon on the basis of changes in renal hemodynamics would demand changes in glomerular filtration rate of greater magnitude than are generally thought to occur.

There is no doubt that osmotic diuresis associated with the excretion of glucose does occur in the diabetic, but evidently this is not the only physiologic mechanism by which diuresis may be induced in such persons. Renal regulatory mechanisms play an important part in determining the rate at which diabetics excrete water, glucose, and electrolytes. The diuresis of stress occurs in the diabetic whether glucose is present in his urine or not.[14] When such a diuresis is induced at a time when the glucose concentration and the specific gravity of the urine are below the maximal level, the excretion of glucose, water, electrolytes and ketones rises in parallel, without important changes in their concentrations relative to each other, and in spite of the fact that the blood glucose concentration may be falling steadily. This phenomenon also is most readily explained on the basis of changes in renal tubular function. Although the adrenal steroids may play a part in the mediation of these changes, the exact neuro-humoral mechanism which is involved remains to be elucidated.

Because of the lability of the human blood glucose concentration and its lack of correlation with other chemical, physical, and symptomatic indicators of bodily function, great caution must be exercised in the clinical evaluation of random blood glucose determinations. Low levels of blood glucose and rapid falls in glucose concentrations may occur in both nondiabetic and diabetic individuals without being accompanied by the symptoms usually attributed to hypoglycemia. Quite commonly normal persons have been observed to be alert, active, and asymptomatic during a morning in which their blood glucose levels lay between 40 and 50 mg. per 100 cc. Conversely, diabetic persons with a hyperglycemia as great as 300 mg. per 100 cc. may exhibit no disturbance of fluid balance and no untoward symptoms in the absence of stress; whereas during stress situations the same persons may have a marked polyuria, glycosuria, and hyperketonemia at much lower blood glucose levels.

The effects of environmental stresses similarly limit the diagnostic value of the glucose tolerance curve. In nondiabetic persons a flat glucose tolerance curve has been described as occurring in persons who suffer from symptoms of anxiety, tension, asthenia and fatigue. These symptoms have been regarded as the effects of functional hypoglycemia.[26] However, it appears that a

flat glucose tolerance curve and a low level of the blood glucose may be readily produced in otherwise normal individuals in response to stress situations which make them anxious and tense. Since chronic fatigue is a usual concomittant of anxiety, whether or not hypoglycemia is also present, it is probable that when fatigue and hypoglycemia occur together in an anxious individual they are parallel phenomena which are not causally related. Abnormally prolonged and clearly "diabetic" glucose tolerance curves probably could be produced also in normal individuals in an appropriate setting of stress. Changes in such a direction were seen in some of our studies.

As we have pointed out elsewhere, it may be profitable to look upon the diabetic not as an individual who is in constant danger of being harmed by the toxic effects of a high blood glucose level, but rather as an individual who is constantly protecting himself from the threat of a low blood glucose level by continually utilizing adaptive processes designed to conserve glucose and to diminish its utilization by the muscles. Such adaptive processes are classically appropriate to starvation, or to settings of stress which tend to cause a depression of the blood glucose. Their appearance in diabetic persons is consistent with what we know of their life histories, the setting in which their illness occurs and the symptoms associated with it.

SUMMARY

The reaction of humans to stressful life experiences may include changes in the concentration of glucose in their circulating blood. These changes are of greater magnitude in persons with diabetes mellitus than in healthy persons.

In the post-absorptive individual the blood glucose usually falls during stress. As the fall occurs there is a rise in the concentration of circulating ketone bodies. The fall in the blood glucose may be of sufficient magnitude to lead to hypoglycemia, but usually it is arrested before hypoglycemic levels are attained. In persons with diabetes mellitus the associated rise in blood ketones is sometimes of such magnitude that it is an important factor in the development of ketoacidosis.

In individuals in the post-absorptive state a rise in blood glucose is a less common response to stress situations, and appears to occur only in settings of intense fear or anger.

In both diabetic and nondiabetic persons, changes may occur in the response to ingested or injected glucose in association with the other changing reactions of the individual to situations in his environment.

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DISCUSSION

DR. ARTHUR R. COLWELL *(Chicago)*: Doctors Hinkle and Wolf should be commended for their efforts to obtain data on the relationships between emotional stress and sugar metabolism. The problem is a fascinating one, which is of considerable practical as well as theoretical importance. There is quite a bit of collateral evidence available which should be reviewed in this connection.

Several questions occur to me in my attempts to seperate the actual observations from the interpretations of this report. I feel that it is somewhat hazardous to draw firm conclusions from the behavior of the blood or urine sugar or ketone levels in a given morning or afternoon. Clinical experience indicates how easily these levels may change, even in so-called neutral situations, and especially in severe diabetes. Without food and after fairly large depot insulin dosage they would be expected to fall, of course, even though insulin was deferred on the morning of the experiment. But that behavior may vary from day to day in the same patient. In the diabetic, at least, I think we should have more hours of stable behavior, or more mornings of neutral conditions for comparison before trying to interpret the effects or mechanisms of stress. Also, could not the rising blood ketone levels have been due to continued fasting rather than the imposition of emotional stress?

Here, as usual, adequate controls are of vital importance. Before the effects of an experimental maneuver can be determined it must be shown that there would be no change unless the maneuver was applied, then that a uniform response was obtained. I hope that Dr. Hinkle will extend and amplify these important studies. Their difficulty is appreciated by all who have worked in the field.

DR. ARTHUR A. HEROLD, SR. *(Shreveport, La.)*: In my own personal experience, I have found hyperglycemia appear on two occasions when I was subjected to stress. Two years ago after the death of my brother, my blood sugar was 168. I took a small amount of insulin for two months. Later, after the death of a surgical colleague, my blood sugar was 216. Again, I began taking insulin but recently I was able to discontinue it.

I have also seen this phenomenon in some of my patients. On asking those who showed a flare-up with high blood sugar about their lives, I found that they had frequently been under unusual stress and strain.

DR. FRANCIS D. W. LUKENS *(Philadelphia)*: I would just like to ask Dr. Hinkle whether he has ever tried to reproduce any of these phenomena with the use of adrenergic or cholinergic agents.

DR. LAWRENCE E. HINKLE, JR. *(Closing)*: In measuring the concentration of glucose in human blood, which is known to be affected by many factors, one cannot be too careful about the question of control. I can only say that we have tried to arrange our experiments in such a manner that the only pertinent variable factor was the content of the situation in which the subject found himself. It is quite true, as Dr. Colwell has pointed out, that the longer-acting insulins have some effect upon the blood glucose level even after twenty-four hours. That this is not responsible for the large falls which occurred in some of the diabetics during stress situations is evident from the fact that no such falls occurred in the same individuals during the control studies. Similar falls also occur during stress situations in nondiabetics, in whom there is no question of the effect of exogenous insulin.

In answer to Dr. Herold's comments, I may say that the clinical experience which he has recounted is quite similar to many which we have observed. As I have pointed out, the initial response of the post-absorptive individual to stress is a transient fall in blood glucose; but if a diabetic under stress continues to ingest glucose, his hyperglycemia is magnified rather than diminished.

In answer to Dr. Lukens' question, we have not attempted to reproduce these phenomena by the administration of drugs to intact individuals, although of course many others have administered such substances as epinephrine and cortical steroids to diabetics, and have made extensive studies. However, I doubt that this is just the way in which I would go about trying to elucidate the mechanisms involved.

ABSTRACTS

ALLEN, R. K.; ROSENAK, B. D.; AND PERMER, E. (*Dept. of Gastroenterology, Indianapolis Gen. Hosp., Indianapolis, Ind.*): Aberrant pancreatic tissue in the stomach. Gastroenterology *21*:148-53, May 1952.

A case of aberrant pancreatic tissue occurring in the stomach is reported. Seven cases have been collected from the American literature since the report of Busard and Walters. This makes a total of 550 reported cases, including that of the authors. Classification and origin of aberrant pancreatic tissue is briefly reviewed.

ANFINSEN, CHRISTIAN B.; BOYLE, EDWIN; AND BROWN, RAY K. (*Nat. Heart Inst., Nat. Institutes of Health, U.S. P. H. S., Bethesda, Md.*): The role of heparin in lipoprotein metabolism. Science *115*:583-86, May 30, 1952.

The authors report on a series of experiments undertaken to purify and define the components of the system which effects clearing of lipemic plasma after administration of heparin. Perfusion experiments on rats indicated that material in plasma in Fraction IV-1 is converted into the clearing factor under the influence of a tissue catalyst and in the presence of heparin. Of the tissues tested, heart and lung are most active in carrying out this conversion.

The clearing factor itself falls into the ultracentrifugal globulin fraction of the plasma, chiefly Fraction III-1,2,3, is destroyed by heat, withstands dialysis and lyophilization, and appears to be enzymatic in nature. Further studies indicate that the clearing actor requires a "coprotein" acting in the capacity of acceptor or stimulator in the clearing system and present in the nonlipoprotein portion of Fraction III-0 of the plasma proteins.

A tentative scheme depicts the conversion of a component of plasma (Fraction IV-1) to clearing factor under the catalytic influence of a soluble tissue substance in the presence of heparin. The role of heparin in this reaction is obscure, but there is evidence heparin occurs as a tightly bound prosthetic group of clearing factor. The clearing factor is pictured as catalyzing the physical or chemical redistribution of plasma lipids in such a way that turbidity is reduced and a reorientation of plasma lipoproteins is brought about, with a decrease in larger or higher S_f components and an accumulation of smaller or lower S_f components. Further study into the mechanism of lipid labilization is under way.

ANNOTATIONS (*England*): Timing of insulin. Lancet *1*: 553, March 15, 1952.

The author comments on the timing of insulin injections before the intake of food in order to insure the proper hypoglycemic effect, thereby reducing postprandial hyperglycemia and glycosuria.

ANONYMOUS *(England)*: Is bread good for diabetics? Brit. M. J. *1*:558, March 8, 1952.

The question in the title is answered in the affirmative, with a discussion of the carbohydrate and protein content of bread.

ARDUINO, FRANCISCO *(Rio de Janeiro)*: Insulin in diabetes. Arquivos de clinica *12*:95-97, 1951.

The author reviews the use of different insulins and of diet in 200 cases of diabetes. Protamine zinc insulin, unmodified, and NPH insulin are discussed, as are the indications for the insulin mixtures.

AZERAD, E.; DE BRUX, J.; NATAF; AND ALAGILLE *(Paris)*: A pathological and histochemical study of the intercapillary glomerulohyalinosis developing in diabetics (Kimmelstiel and Wilson's syndrome). Presse méd. *82*:1733-35, December 25, 1951.

Renal glomerulohyalinosis (a term preferable on histochemical grounds to that of intercapillary glomerulosclerosis of Kimmelstiel-Wilson) is common in aged diabetics, especially in women. Clinically, it is characterized by a tetrad including albuminuria (often high), more or less mild edema, azotemia, and arterial hypertension to which retinitis is related. In a few cases an endocrine syndrome was noted (stigmata of hypothyro-pituitarism), but its connection with Kimmelstiel-Wilson's syndrome is questionable. The course of the disease is fatal within a rather short period of renal and cardiac insufficiency. Pathologically there is a development of hyalinosis in the glomeruli of the kidney. The hyalin substance is a stage in the depolymerization process of the fundamental substance. A noteworthy fact is that in certain cases the depolymerization is replaced by or close to a repolymerization area represented by sclerotic tissue. Such changes are related to chemical transformations dependent on the enzymatic and hormonal system. With a deeper knowledge of these facts it would be possible to make the diabetes problem clearer.

BACHMAN, CARL *(Sch. of Med., Univ. of Pennsylvania, Philadelphia)*: Diabetes mellitus and pregnancy, with special reference to fetal and infantile loss. Am. J. M. Sc. *223*:681-93, June 1952.

The author reviews the signficant publications relative to diabetes mellitus and pregnancy which have appeared since 1946, when Eastman comprehensively surveyed the literature.

Since diabetes is encountered approximately once in every 500 pregnant women, a figure coinciding with the estimated incidence of diabetes in all women of childbearing age, the author concludes there is no significant sterility among diabetic women under modern conditions. Correspondingly, the undertaking of pregnancy by a diabetic woman has become hazardous for her principally, and perhaps only, if her disease has been established for more than 25 years or if its medical control has not been uniformly satisfactory. In these instances the dangers of vascular accidents or of gestational toxemia arise because of the likelihood of a prematurely aged cardiovascular system. With pregnancy, most women exhibit a moderate lowering of the renal threshold for glucose and alteration in the requirement for insulin, varying with the trimester and generally subsiding very rapidly during or following delivery.

Despite the considerable improvement in recent years in fetal and infant salvage, the major problem in diabetic pregnancy is still the high fetal and neonatal loss (more than five times the "standard"), especially during the late months of gestation, parturition, and the early neonatal period. Contributory to this loss are maternal toxemia, spontaneous premature labor, and fetal gigantism, hydramnios, prematurity, and congenital malformations.

Whatever the basis for the deleterious effect of diabetes upon pregnancy, the risk rises steadily after the 32nd week; attempts have been made to circumvent it by (a) the termination of gestation at or about the 36th week; (b) the performance of cesarean section for delivery (to obviate the intrapartal death of one fetus in six during labor or vaginal delivery; and (c) meticulous care of the newborn as though it were a premature baby regardless of its actual age, the baby being placed in a constant temperature incubator under oxygen and in a position favoring postural drainage. The value of adjunctive therapy of the diabetic pregnant woman with increasing doses of estrogen and progesterone, as recommended by White, remains debatable.

BASTENIE, P. A.; AND KOWALEWSKI, K. *(Brussels, Belgium)*: Studies of the double and triple intravenous tolerance tests in normals, diabetics, in patients with liver disease and in those treated with cortisone. Acta gastroenterol. belg. *14*:201-22, April 1951 [Abstr. from Am. J. Digest. Dis. *18*:317, October 1951].

The studies indicated in the title showed that the repeated tolerance test leads to terminal hypoglycemia in normal subjects. It amplifies the abnormality of the hyperglycemic response obtained in liver disease, in diabetes, and under high-dosage cortisone therapy.

BENCOSME, SERGIO A. *(Dept. of Pathology, Univ. of Ottawa, Canada)*: Studies on the methods of staining the islet cells of the pancreas. Arch. Path. *53*:87-97, January 1952.

A systematic investigation of the various methods available for the cytological study of the islets of Langerhans of the pancreas resulted in the modification and combination of a small group which proved to be suitable for the detailed study of the normal, pathologic, embryonic, or adult pancreas. It was found that Masson's trichrome stain

could be developed into an excellent survey stain that not only clearly differentiated alpha, beta, and delta cells but also detected simultaneously all of the cytoplasmic elements that may be demonstrated more clearly by other methods. Both the Masson trichrome and the Gomori method can be applied successfully to counterstain differentially the preparations in which the Golgi apparatus has been shown by the Aoyama technic, or to counterstain argentaffin preparations done by Roger's, Foot-Laidlaw's, and Fontana's technic. The Schridde method was used to demonstrate mitochondria. These various methods used alone and in combination allow unusually complete and exact observations to be made on the pancreas.

BLACK, D. A. K.; AND MILNE, M. D. *(Dept. of Med., Univ. of Manchester, Manchester, England):* Experimental potassium depletion in man. Lancet *1*:244-45, February 2, 1952.

The authors produced a state of potassium depletion which, as judged by serum levels and subsequent retention of potassium, is comparable to that described after diabetic ketosis or after surgical operations. There were no serious clinical symptoms, and it is doubted whether potassium depletion of this degree can account for some of the symptoms which have been ascribed to it. It is the authors' view that moderate degrees of potassium depletion should be controlled by oral potassium and that intravenous potassium therapy, with its risk of cardiac arrest, should be reservd for patients with very low serum-potassium levels and associated muscular palsy who cannot take potassium by mouth.

BLACKWELL, CLAUDE C. *(Birmingham, Ala.)*: Islet-cell adenoma with hyperinsulinism. Am. J. Surg. *83*:165-69, February 1952.

A brief review of the incidence, pathology, symptomatology, and treatment of islet-cell tumors is presented. A case of the successful surgical removal of an islet-cell adenoma of the pancreas is reported.

BOLLMAN, JESSE L.; FAZIO, ANTHONY N.; AND FAULCONER, ALBERT, JR. *(Rochester, Minn.):* Some factors influencing the effects of anoxic anoxia. Anesthesiology *12*:420-30, July 1951.

The ability of rats to withstand the acute effects of exposure to an atmosphere containing 4.5 to 6 per cent oxygen is definitely diminished by acute anemia, hypoglycemia, or hyperthyroidism. Hypothyroid rats and infant rats are more resistant than normal adult rats to the acute effects of anoxic anoxia. The administration of glucose did not appear to alter the susceptibility of rats to the effects of anoxia.

BONDY, PHILIP K. *(Atlanta, Ga.):* Office management of the diabetic patient. J. Tennessee M. A. *45*:227-29, June 1952.

It is the author's opinion that the majority of diabetic patients need not be hospitalized to be introduced to a regimen of control. It is his feeling that this is more nearly accomplished on an ambulant basis, in as simple fashion as possible. The office management of the average patient is such as to make it entirely feasible in the hands of the family doctor.

BRACCI, ULRICO; AND LORENZINI, LUCIANO: The glycemic curve following oral intake of glucose in patients who have had total gastrectomy. Gior. ital. chir. 7:149, 1951 (Abstr. from Surg., Gynec. & Obst. *94*:40-41, January 1952).

The authors studied the blood sugar curve after giving glucose orally in 12 cases in which total gastrectomy had been performed. In 50 per cent, hyperglycemic curves were obtained. A true hypoglycemia was never observed, (the lowest recording was 70) but the curve usually dropped below the starting point in the majority of cases. Patients complained of hunger accompanied by general weakness. These symptoms were considered to be due to a relative hypoglycemia even though not an absolute one. Reference is made to the modification of the absorption of carbohydrate in patients who had gastric surgery.

BRADY, ROSCOE O.; AND HEDGES, THOMAS *(Endocrine Sect. of the Med. Clin. and the Dept. of Ophthalmology, Hosp. of Univ. of Pennsylvania, Philadelphia):* Lack of effect of parahydroxypropiophenone in hyperophthalmopathic Graves' disease and diabetes. J. Clin. Endocrinol. & Metabolism *12*:604-06, May 1952.

Recent reports concerning the ability of parahydroxypropiophenone (PHP) to inhibit the pituitary production of gonadotropin, thyrotropin, and somatotropin stimulated investigators in the United States to attempt verification of these assertions. Their reported results have al-

most universally failed to confirm the claims. Two patients with thyrotoxicosis and coexisting diabetes experienced no change in their insulin requirement. One patient (white male, aged 55), whose initial BMR was —9 per cent, had a slight reduction in protamine zinc insulin requirement from 30 to 24 units per day; whereas another (white female, aged 57) found it necessary to increase her daily insulin from 17 units to 20 units of protamine zinc insulin and 10 units of regular insulin while receiving 1,800 mg. of PHP per day.

BRODRIBB, H. S.; MCMURRAY, J.; AND SCOTT, L. G. *(Hastings Group of Hosps., Hastings, England):* Two cases of diabetes mellitus in infants under 1 year. Brit. M. J. *1*:1060-61, May 17, 1952.

Two cases of diabetes mellitus which began in infants under one year old are described. The first had a gradual onset, which followed immunization, and was comparatively mild. The second was acute and severe and presented pulmonary symptoms and signs; the blood sugar was 1,160 mg. per 100 cc., the highest recorded under the age of one year. Both patients survived and continued well on two doses of soluble insulin daily.

BROWN, RANDOLPH K.; MOSELEY, VINCE; PRATT, T. DENNIE; AND PRATT, JOSEPH H. *(Pratt Diagnostic Clin., New England Center Hosp., Boston)*: Early diagnosis of cancer of the pancreas based on the clinical and pathological study of one hundred autopsied cases. Am. J. M. Sc. *223*:349-63, April 1952.

Early diagnosis of cancer of the pancreas is imperative if surgery is to hold hope of cure. Early pancreatic cancer gives a vague clinical picture; the combination of nondescript upper abdominal pain and weight loss with otherwise negative findings justifies exploratory laparotomy. Pancreatic cancer is about one-fourth as frequent as gastric cancer, occurs predominantly after age 40, and is two to three times as frequent in males.

Cardinal indications of absence of pancreatic juice from the intestine are a massive bulkiness of the stools and the presence of visible fat, resembling butter or cream, on the surface of the stools or in the surrounding fluid, pathognomonic evidence of pancreatic disease. Significant microscopic finding in the stools is the presence of large numbers of undigested, well-preserved muscle fibers after the patient has been placed on a diet with 100 to 150 grams of finely chopped beef or ham given raw or lightly broiled each day.

The secretin test demonstrates pancreatic juice deficiency in most cases if the technic of Agren and Lagerlöf is followed. About 40 per cent of cases have an elevated serum lipase and serum diastase. About 20 per cent of cases exhibit transient glycosuria; 10 per cent, hyperglycemia. Definite diabetes is infrequent.

BROWNELL, KATHARINE A.; HARTMAN, FRANK A.; AND LIU, TSUNG Y. *(Dept. of Physiol., Ohio State Univ., Columbus):* Gluconeogenic and lipid effects of adrenal secretion. Am. J. Physiol. *167*:605-16, December 1951.

The total blood was collected for several hours from the left adrenal in dogs anesthetized with Nembutal or ethyl ether and desensitized with Novocain. Blood from a donor replaced the loss. The plasma was extracted with ethylene dichloride and the hormones finally taken up in 5 per cent alcohol in 0.9 per cent sodium chloride solution. The gluconeogenic hormone content was determined by its ability to cause deposition of glycogen in the liver of adrenalectomized mice starved 24 hours, whereas the lipid activity was determined by the ability to cause deposition of lipid in the liver of similarly prepared mice. Assays of hormone were based on unit of time rather than quantity of blood. The amount of gluconeogenic hormone secreted per unit of time varied greatly from one individual to another, but there was always some secretion. A few dogs showed no secretion of lipid hormone. There was great range in amount among the others. The lipid hormone content of arterial blood was below the limit of sensitivity of our test. Cessation of blood flow through the adrenal for a considerable period sometimes reduced the secretion of both gluconeogenic and lipid hormones when flow was resumed.

BUTTARNI; AND BARONCHELLI: Hepatoprotective and hypoglycemic action of drugs used rectally. Gior. clin. med. Page 917, August 1951 [Abstr. from *Prensa méd. argent.* 39:39, January 4, 1952].

The authors claimed that rectal administration of insulin, vitamin B_1, vitamin E, and methionine exerted a protective action on the lives of diabetics.

BYERS, SANFORD O.; AND FRIEDMAN, MEYER (*Harold Brunn Inst. for Cardiovascular Res., Mount Zion Hosp., San Francisco*): Production and excretion of cholesterol in mammals. VII. Biliary cholesterol: Increment and indicator of hepatic synthesis of cholesterol. Am. J. Physiol. *168*:297-302, February 1952.

The rate of biliary excretion of cholesterol in the rat was found to be dependent upon the rate of hepatic synthesis of cholesterol. This suggested that bile cholesterol represents an increment of the cholesterol synthesized in the hepatic cell itself. The measurement of biliary cholesterol excretion may be employed as a means of assaying the hepatic rate of cholesterol synthesis.

CARDONNET, LUIS J. (*Rosario, Argentina*): Diabetes and pregnancy. Revista del Círculo médico de Paraná September 1951.

A review containing data on current trends in treatment of the pregnant diabetic and in follow-up of the child.

DE CASTRO, A.; AND TEIXEIRA, WALTER (*Rio de Janeiro*): Thioderivatives and hyperthyroidism. Medicina —cirurgia—farmacia *190*-191:67-88, February-March 1952.

In four cases of hyperthyroidism and diabetes mellitus, the control of the diabetes was made easier by the use of propylthiouracil for the thyroid condition. In every case, the dose of insulin could be materially reduced.

CHOLST, MORTIMER R.; SCHILBACK, HAROLD F.; HANDELSMAN, MILTON B.; AND LEVITT, LEON M. (*Depts. of Ophthal. and Med., State Univ. of New York Coll. of Med., and Long Island Coll. Hosp.*): The response of the retinal vessels to Priscoline in various vascular conditions. Am. J. Ophth. *35*:191-95, February 1952.

The effect of Priscoline on retinal circulation was studied in 20 cases including 4 cases of diabetes without retinopathy. All showed good vasodilation.

CHOLST, MORTIMER R.; SCHILBACK, HAROLD F.; HANDELSMAN, MILTON B.; AND LEVITT, LEON M. (*State Univ. of New York Coll. of Med., New York City and Long Island Coll. Hosp.):* The response of the retinal vessels to Priscoline in diabetes mellitus. Am. J. Ophth. *35*:375-80, March 1952.

In 27 cases of diabetes, the response to intravenous administration of Priscoline, as noted by its effect upon the angioscotoma, was as follows: 12 cases responded poorly, 5 cases indicated a fair response, and 10 cases a good response.

COMFORT, MANDRED W. (*Div. of Biometry and Med. Statistics, Mayo Clinic, Rochester, Minn.*): Pedigree of a family with hereditary chronic relapsing pancreatitis. Gastroenterology *21*:54-63, May 1952.

The pedigree of a family in which hereditary transmission of chronic pancreatitis has occurred is presented. The most probable interpretation of the pedigree is that the disease in this family is due to an autosomal dominant gene.

CORDIER, D.; CORDIER, G.; DUVEAU, A.; AND LEMARCHANDS, H. (*Lyon, France*): Changes in hepatic phosphorylysis of glycogen during ischemic shock ("tourniquet shock"). Comptes rendus des Séances de la Société de biologie *145*:1546-48, October 1951.

The ischemic shock modifies the process of phosphorylation at the level of the hepatic cells of the rat. The difficulty is manifested as in traumatic shock, by a marked slowing of hepatic phosphorylysis of glycogen.

CREASEY, N. H.; AND GRAY, C. H. (*Dept. of Chemical Pathology, King's Coll. Hosp., London):* Enzymes concerned in the synthesis of glycogen from glucose in the brown adipose tissue. Biochem. J. 50:74-81, November 1951.

Hexokinase, phosphoglucomutase, and phosphorylase have been demonstrated in extracts of the brown adipose tissue of the rat. The phosphoglucomutase of brown adipose tissue requires magnesium ions for its optimum activity and is inhibited by sodium fluoride and by high concentrations of glucose-1-phosphate. Extracts of the brown adipose tissue of the rat contained supplementary enzyme which, in conjunction with phosphorylase a, catalyzed the synthesis from glucose-1-phosphate of a branched polysaccharide similar to glycogen.

DICKENS, F.; AND GLOCK, G. E. *(Courtauld Inst. of Biochemistry, Middlesex Hosp. Med. Sch., London):* Direct

oxidation of glucose-6-phosphate, 6-phosphogluconate, and pentose-5-phosphates by enzymes of animal origin. Biochem. J. 50:81-95, November 1951.

A direct oxidative pathway, distinct from the glycolytic route, for the oxidation of d-glucose-6-phophate, 6-phospho-d-gluconate, and d-ribose-5-phosphate, has been demonstrated in animal tissues and shown to resemble closely that previously described for yeast. Hexosemonophosphate and 6-phosphogluconate are actively oxidized by extracts of liver (horse, rat, and rabbit), brain (rat and rabbit), and rat-liver carcinoma. Skeletal muscle (rat and rabbit) and Rous's sarcoma of the fowl possess weak activity.

DILL-RUSSELL, A. S. *(King Edward VII Hosp., Windsor, England):* Pancreaticogastrostomy. Lancet *1*:589-90, March 22, 1952.

Pancreaticogastrostomy seems to be the most satisfactory method of dealing with the pancreatic duct in operations for carcinoma in this region, although it can, of course, have no effect on the ultimate prognosis.

DREILING, DAVID A. *(Mt. Sinai Hosp., New York City):* Studies in pancreatic function: IV. The use of the secretin test in the diagnosis of tumors in and about the pancreas. Gastroenterology *18*:184-96, June 1951.

Diabetes mellitus is a frequent concomitant of pancreatic malignancies. Diabetes per se produces no alteration in the external secretion of the pancreas. The occurrence of abnormal secretin responses in a diabetic, therefore, is presumptive evidence of pancreatic tumor or pancreatitis. Tumors contiguous to the pancreas produce no alteration in pancreatic secretion.

DREILING, DAVID A.; RICHMAN, ALEXANDER; AND FRADKIN, NATHAN F. *(Mount Sinai Hosp., New York City):* The role of alcohol in the etiology of pancreatitis: A study of the effect of intravenous ethyl alcohol on the external secretion of the pancreas. Gastroenterology 20:636-46, April 1952.

The association of alcoholism and pancreatic disease is significant and not casual. The literature on this subject is reviewed and discussed. Alcohol administered intravenously in man to a point of intoxication does not result in an increase in pancreatic secretion. Five patients with chronic pancreatitis so treated showed no immediate or delayed effects. A hypothesis is presented to explain the etiologic role of alcohol in the precipitation of attacks of pancreatitis, in which it is suggested that the oral intake of alcohol causes the pancreas (via the secretin mechanism) to secrete a large volume of pancreatic juice against an obstruction to the flow of the secretions (by spasm and edema of the papilla). Rupture of the finer radicles of the pancreatic tree may result from the sudden increase in intraductal pressure. Chronic relapsing pancreatitis is considered the end result of many such episodes.

DREILING, DAVID A.; DRUCKERMAN, LEONARD J.; AND HOLLANDER, FRANKLIN *(Mount Sinai Hosp., New York City):* The effect of complete vagisection and vagal stimulation on pancreatic secretion in man. Gastroenterology 20:578-86, April 1952.

Pancreatic function has been studied in patients subjected to complete bilateral vagisection (as a result of esophagogastrectomy), and the responses have been compared with those in nonvagectomized individuals. Vagisection in man does not influence the response of the pancreas to a fixed dose of exogenous secretin in regard to volume secretion, bicarbonate concentration, or amylase output. In response to insulin hypoglycemia, however, the enzyme response is absent, as are the other two factors. On the basis of the findings it is concluded that postvagotomy diarrheas are not due to diminished pancreatic secretion, nor does the study afford any other evidence in regard to pancreatic secretion which negates the use of vagal section in the therapy of peptic ulcer, ileitis, and ulcerative colitis. The utilization of the pancreatic response to insulin hypoglycemia is suggested as a test for vagal integrity under special circumstances.

EDITORIAL: *(Boston)* Salute to *Diabetes.* New England J. Med. *246*:387-88, March 6, 1952.

The new publication *Diabetes* and its various sections are described in an editorial.

ELMAN, ROBERT; AND LIEBERMAN, ZELIG H. *(Dept. of Surg., Washington Univ. Sch. of Med., and Barnes Hosp., St. Louis):* The pancreas: Contributions of clinical interest in 1950. Gastroenterology *21*:24-53, May 1952.

The authors review the significant contributions to the medical literature of clinical interest in 1950. They cover the subjects of acute pancreatitis, chronic pancreatitis, carcinoma of the pancreas, fibrocystic disease of the pancreas, pancreatic cysts, pancreatic function tests, the association of pancreatitis with ulcerative colitis, and experimental studies.

ENGEL, FRANK L.; VIAU, ALBERTO; COGGINS, WILLIAM; AND LYNN, WILLIAM S., JR. *(Atlantic City):* Diabetogenic effect of growth hormone in the intact force-fed adrenocorticotrophin treated rat. Endocrinology *50*:100-14, January 1952.

Adult male and female rats force-fed a high-carbohydrate liquid diet consistently developed hyperglycemia and glycosuria while receiving both ACTH and anterior pituitary growth hormone. Glycosuria was absent or inconstant on treatment with either hormone alone unless excessive diet volumes were fed. In one rat on a fixed dose of ACTH, glycosuria appeared to vary directly with the dose of growth hormone, whereas the reverse did not appear to be true. The significance of these results is discussed with regard to the comparative roles of the pancreas, the adrenal cortex, and the capacity for growth in determining the diabetogenic effect of growth hormone in the rat. It is suggested that a level of adrenal activity high enough to prevent the full expression of the growth response to growth hormone may be necessary before a diabetogenic effect of growth hormone becomes apparent and that the high functional reserve of the pancreas may be responsible for the failure to develop permanent diabetes.

ENGEL, RUDOLF; HALBERG, FRANZ; ZIEGLER, MILDRED; AND MCQUARRIE, IRVINE *(Minneapolis):* Observations on two children with diabetes mellitus and epilepsy. Journal Lancet *72*:242-48, May 1952.

Case reports on two children with the clinical syndrome of diabetes and epilepsy are presented. Certain practical and fundamental aspects of the state after hypoglycemic brain damage are considered. In diabetics with epilepsy, the assumption that all seizures result from insulin-induced hypoglycemia is unwarranted. Genuine epileptic seizures are infrequently associated with hypoglycemia in these patients, who have apparently developed a chronic convulsive state as a result of permanent brain damage. Neither hypoglycemia nor hyperglycemia, per se, is correlated with most of their seizures. There is less 2½ per second wave and spike activity in hypoglycemia than in hyperglycemia. Hyperglycemia is associated with relatively low and hypoglycemia with relatively high blood eosinophil counts.

ENGELSON, G. *(Gothenburg, Sweden):* Choline therapy of diabetes (preliminary report) Svenska Lakartidn. *48*:94-99, 1951.

The author believed that administration of choline might be beneficial in certain cases of diabetes with late complications such as nephropathy and retinopathy. In the majority of the cases which he treated, no change in the condition took place.

FISHER, PETER; AND KLEINERMAN, JEROME I. *(Philadelphia Gen. Hosp., Graduate Sch. of Med., Univ. of Pennsylvania, Philadelphia):* Total oxygen consumption and metabolic rate of patients in diabetic acidosis. J. Clin. Investigation *31*:126-30, January 1952.

Total oxygen consumption and metabolic rate were studied in 11 patients in diabetic acidosis and in 7 nondiabetic controls. There is a marked and highly significant increase statistically in the metabolic rate of the group in diabetic acidosis compared with expected normal values and with values found in the nondiabetic controls. In a series of 5 determinations on apparently healthy young males hyperventilation per se showed no significant effect on the oxygen consumption or basal metabolic rate. The possible significance of these findings is discussed.

FOURACRE BARNS, H. H.; AND MORGANS, M. E. *(Obstetric and Med. Units, Univ. Coll. Hosp., London):* The conduct of pregnancy complicated by diabetes mellitus. Brit. M. J. *1*:1058-60, May 17, 1952.

A fetal salvage rate in a small series of diabetic pregnancies was 20 out of 24. The results were thought to justify the pregnancy's not being prematurely terminated. Hormone therapy was used. The opinion is for-

warded that, in terms of results achieved, the co-operation between physician, pediatrician, and obstetrician is more important than the hormone therapy the patients received.

FRIEDMAN, MEYER; AND BYERS, SANFORD *(Harold Brunn Inst. for Cardiovascular Res., Mount Zion Hosp., San Francisco):* Production and excretion of cholesterol in mammals. VI. Bile acid accumulation in production of hypercholesteremia occurring after biliary obstruction. Am. J. Physiol. *168*:292-96, February 1952.

Following biliary obstruction, lecithin and bile acid accumulate in excess of plasma. The administration of lecithin intravenously to obstructed animals indicates that lecithin administration did not influence the hypercholesteremia.

On the other hand, marked hypercholesteremia is induced in rats by sodium cholate administration either orally to biliary-obstructed animals or intravenously to intact animals. The view that accumulation of bile acid after biliary obstruction of itself initiates the cholesteremic process is consistent with the concurrent rise in plasma bile acid and cholesterol following bilateral nephrectomy.

Thus, accumulation of bile acid occuring in plasma after biliary obstruction in the rat appears to be responsible for the hypercholesteremia observed after biliary obstruction.

FRIEDMAN, MEYER; BYERS, SANFORD O.; AND ROSENMAN, RAY H. *(Harold Brunn Inst. for Cardiovascular Res., Mount Zion Hosp., San Francisco):* The accumulation of serum cholate and its relationship to hypercholesteremia. Science *115*:313-19, March 21, 1952.

The authors report on a clinical study of hypercholatenia in states of hypercholesteremia. In nephrosis (12 cases), of xanthoma (6 cases), of diabetes (5 cases), myocardia infarction (8 cases), and hypothyroidism (2 cases), all with a serum cholesterol above 300 mg. per 100 cc., an elevated blood cholate level (9 to 44 as compared with normal range of 1.7 to 7.2) was invariably observed; the degree of hypercholesteremia appeared to bear a close relationship to the extent of hypercholatemia. This finding is in accord with experimental work in which cholate accumulation in plasma in such diverse states as biliary obstruction and nephrosis evoked hypercholesteremia. These results suggest that clinical hypercholesteremia may be a phenomenon secondary to an initial derangement of cholate metabolism and indicate that the role of the liver must be kept in mind in any evaluation of the factors involved in the pathogenesis of human hypercholesteremia.

GILBERT, G. A.; AND PATRICK, A. D. *(Dept. of Chem., The Univ., Edgbaston, Birmingham, England):* Enzymes of the potato concerned in the synthesis of starch. 1. The separation and crystallization of Q-enzyme. Biochem. J. *51*:181-86, May 1952.

Potato Q-enzyme has been prepared in crystalline form and with high activity by a method involving precipitation with ethanol at low temperature and low ionic strength. Electrophoretic analysis has been used to follow the course of the purification. Activation of the enzyme by ions has been confirmed, and the effect of temperature on the activity of the enzyme has been examined.

GILBERT, G. A.; AND PATRICK, A. D. *(Dept. of Chem., The Univ., Edgbaston, Birmingham, England):* Enzymes of the potato concerned in the synthesis of starch. 2. The separation of phosphorylase. Biochem. J. *51*:186-90, May 1952.

Potato phosphorylase has been prepared by a method involving precipitation from potato juice with ethanol followed by extraction with zinc acetate and precipitation with ammonium sulfate. The phosphorylase preparation has an activity about nine times greater than that of preparations previously described. No phosphatase, amylase, or Q-enzyme activity has been detected in the product.

GREEN, PAUL; AND WADE, EUNICE *(Winnipeg, Canada):* Determination of true blood sugar using anthrone. Canad. M. A. J. *66*:175, February 1952.

A modification is described for the determination of true blood sugar using Dreywood's anthrone reagent. With this method, permanent calibrations for colorimeters are possible, and the necessity for making fresh reagent daily is overcome.

GROEN, J.; KAMMINGA, C. E.; WILLEBRANDE, A. F.; AND BLICKMAN, J. R. *(Wilhelmina-Gasthuis, Amster-*

dam, Netherlands): Evidence for the presence of insulin in blood serum. A method for an approximate determination of the insulin content of blood. J. Clin Investigation *31*:97-106, January 1952.

The results of a quantitative study of the effect of insulin on the glucose utilization of the isolated rat diaphragm are reported. Although the sensitivity of the isolated rat diaphragm to small amounts of insulin is variable, it can be demonstrated by this method that normal human and dog serums contain a substance which has an insulin-like action on glucose utilization and glycogen synthesis of the isolated rat diaphragm. In serums of patients with diabetic coma and in those of dogs after complete pancreatectomy, the insulin-like activity was either absent or considerably diminished. The increase in the glucose utilization and glycogen synthesis upon the addition of serum may be used as a means of estimating the insulin content of blood. Normal blood serum contains between 6.25 x 10^{-5} and 6.25 x 10^{-4} units of insulin per ml. With this method, accurate diagnosis of "functional" hypoglycemia (two cases) and of islet-cell adenoma (one case) were made. The possibilities and limitations of the method are discussed.

HALL, G. F. M. *(Dept. of Morbid Anatomy, King's Coll. Hosp. Med. Sch., London):* The significance of atheroma of the renal arteries in Kimmelstiel-Wilson's syndrome. J. Path., & Bact. *64*:103-20, January 1952

Two types of glomerular lesions occurring in diabetic glomerulosclerosis, the nodular lesion and the exudative lesion, are briefly described on the basis of the findings in a series of 135 diabetics. The clinical and postmortem findings in 8 cases of Kimmelstiel-Wilson's syndrome dying in uremia are recorded. Gross atheroma, with much narrowing of the renal arteries, was present in all 8 cases. Atheromatous involvement of the large and small branches of the renal artery gives the kidney a characteristic gross appearance. The histologic picture in all 8 cases was distinctive, the predominant feature being ischemic obliteration of vast numbers of glomeruli. Atheroma of the renal arteries has been seen in comparable degree in only one other case which did not show similar clinical and histologic features. In 43 other cases of diabetic glomerulosclerosis there was no other evidence that the renal lesion, uncomplicated by renal artery atheroma, was responsible for death. The pathogenesis of the massive obliteration of glomeruli is discussed, and it is concluded that obliteration results from atheromatous narrowing of the renal arteries superimposed on severe arteriolosclerosis.

HILDES, J. A.; FERGUSON, MARION H.; AND BARTLETT, L.C. *(Depts. of Physiol., Med. Res., and Surg., Univ. of Manitoba, and Winnipeg Gen. Hosp., Winnipeg, Canada):* The water and electrolyte excretion of the human pancreas. Gastroenterology *21*:64-70, May 1952.

The volume and composition of pancreatic juice was studied in a subject with a complete pancreatic fistula during an 11-day period of alimentary starvation, preceded and followed by control periods on oral feeding. During the starvation period, intravenous glucose and amino acids were administered. The 24-hour volume of pancreatic juice was decreased to about 300 ml. per day. Banthine had no apparent effect on the daily volume of fistula juice. The daily urine output was roughly reciprocal to the pancreatic loss. The sodium and potassium concentrations of the pancreatic fluid remained constant and close to the respective serum concentrations, irrespective of the volume of secretion. The chloride concentration was also constant but below that of the serum. The daily urine output of these elements was also roughly reciprocal to the pancreatic loss.

HOLLANDER, FRANKLIN *(Mount Sinai Hosp., New York City):* Comments; Comment on the insulin test for vagal continuity. Gastroenterology *21*:164-65, May 1952.

The author mentions others who have collaborated with him in the development of the insulin test for vagal continuity and decries the growing trend of labeling the test with his name alone.

KASTEN, FREDERICK H. *(Dept. of Zool., Univ. of Texas, Austin):* Comparative histological studies of endocrine glands of yellow and non-agouti mice in relation to the problem of hereditary obesity. Science 115:647-49, June 13, 1952.

The author reports a comparative histological study of endocrine glands (thyroid, adrenal, testes, or ovaries) in yellow obese and nonagouti mice. No significant differences were noted in the thyroid glands, adrenal glands, and testes in the black mice and in the mice carrying the yellow gene; but the ovaries of obese yellow females showed significant differences and abnormalities from those of nonyellow. These ovarian anomalies correlate with earlier reports of low fertility in obese

females and with the fact that onset of obesity coincides with attainment of sexual maturity. Obesity in mice carrying the yellow gene is caused by an increase in food intake and less physical activity. Data presented by the author support the hypothesis that obesity results from a hormonal disorder and upsets normal ovarian function, causing sterility. The possibility that the ovary itself is the site of the hormonal disorder causing obesity is not excluded by this hypothesis.

KEILIN, D.; AND HARTREE, E. F. *(Molteno Inst., Cambridge, England):* Specificity of glucose oxidase (notatin). Biochem. J. 50:331-41, January 1952.

The catalytic oxidation of b-glucose by notatin is much faster than that of a-glucose. Two samples of notatin (Y and Z) which were of equal catalytic activity in the oxidation of b-glucose showed very different activities in the oxidation of a-glucose. Sample Z oxidized a-glucose about eight times faster than sample Y. Manometric study of the oxidation of a-glucose by these samples of notatin indicated that sample Z contained an additional component capable of catalyzing mutarotation. This was confirmed by polarimetric study of the effect of the two samples of notatin on mutarotation of glucose under strictly anaerobic conditions. When notatin Y, which did not influence mutarotation, was used, the rates of the direct oxidations of a- and b-glucose were obtained. The ratio of oxidation rates obtained is b:a = 100:0.64 at 20°. The bearing of this result on the use of notatin for estimation of glucose formation in biological systems is discussed. The oxygen uptake in the presence of notatin is a reliable measure of glucose formation at any temperature if glucose is liberated in the b-form, whereas at 39° the mutarotation is fast enough to insure that the oxygen uptake is a true measure of the rate of appearance of either isomer. If glucose is liberated in the a-form at lower temperatures, the concentration of notatin must be carefully adjusted so that the oxidation of glucose does not limit the rate of the over-all reaction. All eight d-aldohexoses have been tested with notatin. If the rate of oxidation of b-glucose equals 100, the rates of the other sugars are as follows: mannose = 0.98, altrose = 0.16, and galactose = 0.14, whereas allose, gulose, idose, and talose are not oxidized. The high specificity of notatin for b-glucose is indicated by the fact that optical inversion at any carbon atom or substitution in the hydroxyl groups of the substrate either reduces the catlytic activity of notatin to about 1 per cent of its original value or abolishes it altogether. Notatin can now be considered as a specific b-d-glucopyranose oxidase.

KELLNER, AARON *(Dept. of Pathology, New York Hosp.-Cornell Med. Center, New York City):* Lipid metabolism and atherosclerosis. Bull. New York Acad. Med. 28:11-27, January 1952.

A review article.

KERR, ROBERT B.; BROWN, GORDON D.; AND KALANT, NORMAN *(Toronto):* A follow-up study of juvenile diabetics. Canad. M. A. J. 66:97-104, February 1952.

A follow-up study is reported on a group of 81 diabetic patients whose disease began in early childhood or adolescence and had been present for periods up to 28 years. Only 40 per cent of the group had been maintained in reasonably good diabetic control. The remaining 60 per cent were considered as poorly controlled. Of the 81 patients, 49 had demonstrable complications (41 retinopathy, 7 cardiac disease, 11 renal disease, 13 vascular calcification, 8 neuropathy, 8 skin lesions). The incidence of complications increased with duration and with the lack of good control. Twenty-three pregnancies resulted in 9 abortions, 3 fetal and neonatal deaths, and 11 living children. The importance of striving for physiological control of the diabetes is stressed.

LANDMANN, HEINZ R. *(Santa Fe, N.M.):* The differential diagnosis of hypoglycemia. Am. J. Digest. Dis. 19:110-12, April 1952.

A review of the clinical and laboratory studies which have proved helpful in the investigation of hypoglycemia.

LOBO ONELL, C. *(Santiago, Chile):* Study of a new type of insulin (NPH 50) in severe diabetes. Revista chilena de urologia 15:13, March 1952.

Five severe diabetics previously treated with protamine zinc insulin or 2:1 mixtures of regular and protamine zinc insulin were transferred to NPH insulin. In every instance, equal or better control was attained with the new insulin. The final dose of NPH was lower than the dose of protamine zinc insulin being used.

LOGGAN, POWELL B.; AND KLEINSASSER, LEROY J. Surgery of the pancreas; the results of pancreaticoduodenal resections reported in the literature. Surg., Gynec. & Obst. 93:521-43, December 1951.

The authors review resection of the pancreas not only for cancer but also for such benign conditions as pancreatitis and tumors of the islands of Langerhans.

LONG, C. N. H. *(Dept. of Physiol. Chem. Yale Univ., New Haven, Conn.):* The endocrine control of the blood-sugar. Lancet 1:325-29, February 16, 1952.

The author points out that, although the blood glucose level is the result of processes by which glucose is added to the blood and utilized in the tissues, the blood glucose level is maintained within the narrow limits of normal by a close interaction between those metabolic processes and the secretions of certain endocrine organs—notably, the pancreas, anterior pituitary, and adrenals. The rate of utilization of glucose in the tissues and hence the upper limit of the blood glucose level are largely determined by the secretion of insulin. There is valid evidence that the secretion of insulin is increased by a rising blood glucose level, a type of regulation that seems to be admirably adapted to deal with the sudden entry of considerable quantities of glucose into the body. On the other hand, the maintenance of a minimal blood glucose level is the result of a complex interplay between the secretions of the anterior pituitary, the adrenal cortical hormones, and in some instances the hormone of the adrenal medulla. This interplay maintains the blood glucose level in three ways: (1) the discharge of adrenaline makes available any preformed liver glycogen; (2) the release of ACTH augments the secretion of the 11-oxygenated adrenal steroids, one of whose functions is to accelerate the formation of glucose from noncarbohydrate precursors; and (3) the suppression by these steroids of carbohydrate utilization by the tissues. Although the mechanism responsible for the stimulation of anterior lobe function during fasting is obscure, there is little doubt of its occurrence, for in the absence of the anterior lobe of the pituitary the blood glucose soon declines to levels incompatible with life. The contribution of this new knowledge lies in the light that it throws on the chain of events begun when the insulin supply becomes deficient. It is hoped that as our knowledge of the basic activities of these hormones and their interrelationship unfolds, the reason for the widespread incidence of diabetes in man will also be revealed.

LOPES DE ALMEIDA; ARY; AND GROSSMAN, MORTON I. *(Dept. of Clin. Sci., Univ. of Illinois Coll. of Med., Chicago):* Experimental production of pancreatitis with ethionine. Gastroenterology 20:544-77, April 1952.

When ethionine, the ethyl analogue of methionine, was given to dogs, cats, and monkeys, it resulted in the production of acute pancreatitis characterized by focal or diffuse necrosis of the acinar cells, interstitial inflammatory reaction, and fat necrosis. No lesions of the ducts, blood vessels, or islets were seen. Simultaneous stimulation of the pancreatic secretion with food or Urecholine did not significantly augment the effectiveness of ethionine in producing the pancreatitis. In addition to the lesions in the pancreas, it was observed that there were oral and gastro-intestinal hemorrhages, ulcerations of the rectum, and fatty changes in the liver and kidneys. Periodic blood enzyme determinations were made in the dog during the course of ethionine administration. A sharp rise of blood amylase and lipase accompanied the development of the pancreatitis described. Pancreatic secretion was studied under various conditions and at different stages in the production of the pancreatitis. When a single dose of ethionine was given during the course of an acute experiment, impairment of secretion was seen only in the dogs receiving both Urecholine and secretin for stimulation and not in the ones that received only secretin, and the impairment observed was related to enzyme secretion. The volume and bicarbonate output remained unaffected. In contrast to this selective depression on enzyme secretion, the animals which had received ethionine for a number of days showed a tendency toward depression of all components of the pancreatic juice. A comparison between these findings and the histological picture of the pancreas has been made. In the pancreatic juice of dogs at different stages of development of pancreatic damage, active trypsin was not found more frequently or in larger amounts than in normal dogs. Although the mechanism of production of pancreatitis by ethionine is unknown, the possible relationship to interference with protein metabolism is discussed.

MACHADO, JOAO DE OLVEIRA: Acute pancreatitis. Bol. clin. hosp. civ. Lisboa 15:85, 1951 [*Abstr. from* Surg., Gynec. & Obst.; Internat. Abstr. Surg. 93:460, November 1951].

The author reviews the pathology and the symptoms, including pain which is oustanding and may radiate to

the right or left or directly to the back, vomiting occurring without relief of pain, shock and sometimes icterus and hematemesis. In the interstitial type of pancreatitis the symptoms may be minimal. Transitory hyperglycemia and glycosuria may occur. Of all the laboratory methods, amylase and lipase studies begun in the first hours of the disease are most helpful.

MARSH, JULIAN B.; AND HAUGAARD, NIELS *(Univ. of Pennsylvania, Philadelphia):* The effect of serum from insulin-resistant cases on the combination of insulin with the rat diaphragm. J. Clin. Investigation, *31*:107-10, January 1952.

The ability of human serum to influence the combination of insulin with the isolated rat diaphragm has been studied. The combination of insulin with the diaphragm, as measured by its effect on glycogen synthesis, was found to be significantly decreased in the presence of serum from normal or diabetic individuals. The authors have concluded from this that serum contains substances which combine with or inactivate insulin. Serum from insulin-resistant patients appears to contain greatly increased amounts of such substances.

MARSHALL, WALLACE *(Two Rivers, Wis.):* Insulin dosage in diabetics: A simplified method of determining initial insulin dosage in diabetics. M. Times, New York *80*:167-68, March 1952.

In the author's experience one unit of plain insulin will usually lower the blood sugar approximately 3 mg.

MEGEVAND, ALBERT *(Geneva, Switzerland):* NPH insulin in the outpatient clinic. Praxis *41*:343-44, April 17, 1952.

Sixteen patients were transferred to NPH insulin. Seven had previously been treated with mixtures of unmodified and protamine zinc insulin, 5 with a single daily injection of di-insulin, 1 with 2 daily injections of di-insulin, 2 with protamine zinc insulin, and 1 with 2 to 3 daily injections of "vitrum" insulin. In 8 patients the control was decidedly better than that observed with the previous regimens; in 2, it was equally as good; and in 6, it was inferior to previous control. The author concludes that NPH insulin will be ideal in a majority of cases, although in a number of instances, tailor-made individual mixtures will still have to be utilized.

MENOF, P.: Role of vitamin B_{12} in polyneuritis, fatty degeneration and pernicious anemia. South African M.J. *25*:394, June 9, 1951 [Abstr. from J.A.M.A. *147*:791, Oct. 20, 1951].

The author reported a dramatic response in 9 of 11 cases. Treatment of 12 similar patients (7 alcoholic, 4 diabetic, and 1 diabetic and alcoholic) was uniformly satisfactory.

MILLER, MAX; DRUCKER, WILLIAM R.; OWENS, J. E.; CRAIG, JAMES W.; AND WOODWARD, HIRAM JR. *(Western Reserve Univ. Sch. of Med., Cleveland):* Metabolism of intravenous fructose and glucose in normal and diabetic subjects. J. Clin. Investigation *31*:115-25, January 1952.

In three normal subjects, fructose intravenously produced a much greater rise in blood pyruvic acid and a rise rather than a fall in plasma citric acid, as compared with glucose. The fructose disappeared more rapidly from the blood stream during the period of the infusion, since the blood level of fructose increased only half as much as the level of glucose. Similar amounts (less than 10 per cent) of fructose and glucose appeared in the urine.

In 5 diabetic subjects in the absence of insulin, fructose produced the same rise in pyruvic acid as was found in the normal subjects, whereas glucose produced either a slight or delayed rise. Increases in plasma citric acid after fructose administration were similar to those in the normal individuals. The blood disappearance curve of fructose and the amount of fructose excreted in the urine in patients with diabetes were the same as in normal subjects. Fructose administration invariably produced a fall in serum inorganic phosphorus, but a fall did not usually occur after glucose. These studies indicate that (1) the metabolism of fructose differs from that of glucose in both the normal and the diabetic subject, and (2) the metabolism of fructose in the diabetic is similar to that in the normal person even in the absence of insulin. The observations are consistent with the theory that the phosphorylation of glucose to glucose-6-phosphate is impaired in diabetes, whereas the phosphorylation of fructose, which is not influenced by insulin, proceeds at a normal rate.

MONTES, GONZALO *(Bogotá, Colombia):* Effects of phosphoric esters of thiamin and its oral use in the treatment of diabetes. Terapia *9*:114-15, July-September 1951.

The author observed in 4 cases of diabetes that oral administration was followed by a fall in blood sugar. He reported also that rabbits treated either by injection or orally showed a hypoglycemic effect.

PEDERSEN, JORGEN *(Copenhagen):* Course of diabetes during pregnancy. Acta endocrinologica 9:342-64, April 1952.

The material, which was obtained from the Lying-in Departments of Rigshospitalet in Copenhagen, comprises 205 pregnancies among 152 diabetics. Variations were seen in the course of diabetes during pregnancy, 67 per cent showing exacerbation, 13 per cent improvement, and 20 per cent status quo in relation to the prepregnancy state. The alterations in the severity of diabetes took place at 2 typical periods, reaching a peak about the second to the third month and about the seventh month. At the former period an improvement in tolerance, lasting for an average of 2 or 3 months, was commonly observed. The manifestation of this improvement was insulin coma, other insulin reactions, or an improvement in the degree of compensation. When a reduction in the insulin dosage was called for, it amounted to an average of 34 per cent. At the latter period, about the seventh month, there was often a decreased tolerance, manifesting itself as diabetic precoma (acute acidosis of a lesser degree) requiring an increase in the insulin dosage. The decrease in tolerance required an increase in insulin dosage averaging 75 per cent as compared with the dose administered immediately before the alteration in tolerance, and this was the same for patients with and without acidosis. The individual increases in dosage ranged from 4 to 88 I.U. The duration of this reduction in tolerance averaged 2 months. Half these patients exhibited increased tolerance at about the second or third month. The author does not know what causes the typical alterations in the course of diabetes, but the fetal insulin production or carbohydrate consumption cannot be decisive.

PHILLIPS, D. M. P. *(Courtauld Inst. of Biochemistry, Middlesex Hosp. Med. Sch., London, W. 1, England):* The activity of enzymic and acidic digests of insulin. Biochem. J. 50:479-86, February 1952.

Crystalline chymotrypsin, trypsin, and pepsin degrade crystalline insulin to give peptide fractions which show no hypoglycemic activity. Digestion by purified crystalline trypsin causes considerable loss of activity although little nonprotein nitrogen is formed. The remaining activity shown by the whole digests is precipitable at *p*H 5.5 and is probably due to intact insulin still present. Variation of the *p*H of digestion affects the rate but fails to give active fractions. Hydrolysis with 8N and 0.8N hydrochloric acid at low temperatures similarly destroys the activity, and the nonprotein fractions formed during hydrolysis have no activity. Ether, trichloroacetic acid, 5M urea and diisopropyl fluorophosphonate have no appreciable effect on the activity of insulin in periods of contact up to 24 hours.

QUERIES AND MINOR NOTES *(Montana):* Diabetic foods. J.A.M.A. *149*:797, June 21, 1952.

The best low-carbohydrate foods are the vegetables containing 3 per cent and 6 per cent carbohydrate. In large quantities, these are generally cheaper canned than fresh. Next to these, grapefruit, strawberries, and oranges, in season, are the most satisfactory. If these foods are not available, one could use apples in half the quantity of other fruits.

To prepare low-carbohydrate jelly, wash and drain fresh strawberries, add 2 or 3 saccharin tablets, and simmer on a low flame for about 20 minutes. This is a substitute for strawberry jam. Rhubarb jam can be prepared the same way.

QUERIES AND MINOR NOTES *(New Jersey):* Diabetes mellitus. J.A.M.A. *149*:621, June 7, 1952.

The dose of NPH insulin should be increased steadily until an amount is found that will provide satisfactory blood and urine sugar tests in the late afternoon, evening, and night. The dose of regular insulin before breakfast should be continued and may be given either in the same syringe with the NPH insulin or by separate injection. After the dose of NPH insulin has been increased to the level suggested, the dose of regular insulin should be adjusted to the level that will yield good urine and blood sugar tests just before the noon meal. Temporarily, until better control of the situation has been gained, a supplementary dose of regular insulin before the evening meal may be needed.

RAUCH, ROBERT F.; AND STENSTROM, WILHELM K. *(Depts. of Surg. and Roentgen Therapy, Univ. of Minn. Med. Sch., Minneapolis):* Effects of x-ray radiation on pancreatic function in dogs. Gastroenterology 20:595-603, April 1952.

The volume of pancreatic secretion decreased temporarily in 5 dogs with pancreatic fistulas following irradiation. In a few instances there appeared to be a subsequent secondary increase above normal. No definite alteration of the alkalinity of the juice was noted following 400 to 1,000 r of irradiation. In all instances, roentgen therapy with an exposure of 400 or 600 r had a definite depressive effect on the amylase, lipase, and trypsin output of the pancreas. In general, this effect occurred following a 12 to 36 hour delay, and the period of depression was limited to a few days in each animal studied. Similar findings were noted with a second exposure to irradiation. The changes observed in regard to the amylase, lipase, and trypsin output were similar and parallel to each other except for a more persistent depression of trypsin following a second period of irradiation. No organic changes were found histologically in any abdominal organ subsequent to single exposures to 600 r or following repeated exposures to 200 r on alternate days for totals of 800 and 1,600 r.

ROLLAND, C. F. *(Dept. of Therapeutics, Univ. of Edinburgh, Edinburgh, Scotland):* Diabetes mellitus in surgical patients. Brit. M. J. 1:737-40, April 5, 1952.

The problems of the control of diabetes in surgical patients are discussed. Details are given of a series of 300 consecutive surgical diabetics. The majority of the patients are discussed. Details are given of a series of 300 was the most common single disorder. Forty-one of the patients were not known to be diabetic when they were admitted to the surgical wards. The over-all mortality was 9.3 per cent. Diabetic coma was unimportant as a cause of death.

SAYEN, ANN; HORWITZ, ORVILLE; AND STROUD, MORRIS V. *(Peripheral Vascular Section, Edward B. Robinette Foundation, Med. Clin. Hosp. of Univ. of Pennsylvania):* Digital cutaneuous blood flow, cardiac output, blood pressure and pulse rate immediately following the administration of four potential vasodilators. Am. J. M. Sc. 221:667-68, June 1951.

SKF 688A, a dibenamine-like substance; L 08146, a papaverine-like substance; sodium salicylate, and ACTH, in the doses administered, had no immediate measurable effects on digital cutaneous blood flow, cardiac output, blood pressure, pulse rate, or mouth temperature.

SCHWARTZ, HELEN M.; AND LEA, C. H. *(Low Temperature Station for Research in Biochemistry and Biophysics, Univ. of Cambridge and Dept. of Scientific and Industrial Res., England):* The reaction between proteins and reducing sugars in the 'dry' state. Relative reactivity of the alpha- and epsilon-amino group of insulin. Biochem. J. 50:713-16, March 1952.

An investigation has been made of the reaction at 37° between insulin and glucose freeze-dried together from solution at *p*H 7. The rate of reaction has been shown to increase with increasing activity of water to a maximum at which water content is in equilibrium with a relative humidity of approximately 70 per cent and thereafter to decrease again with further increase in water content. The reactivities toward glucose of the alpha-amino groups attached to the terminal phenylalanyl and glycyl residues and of the epsilon-amino groups attached to the lysyl residues of insulin have been determined by the fluorodinitrobenzene method. After 4 days at 65 per cent relative humidity, 70 per cent of the phenylalanyl amino groups, 37 per cent of the glycyl amino groups, and only 21 per cent of the lysyl amino groups had reacted. After 16 days the corresponding figures were 80, 66, and 55 per cent.

SHARP, R. L.; SNAPE, W. J.; AND GILBERT, P. D. *(Depts. of Med. and Radiology, Cooper Hosp., Camden, N. J.):* Fatty metamorphosis of the liver associated with pancreatic calcification; a study by means of needle biopsies of the changes in the liver of a patient treated with dietary and insulin management. Gastroenterology 20:647-52, April 1952.

Needle biopsy of the liver in a patient with pancreatic calcification revealed extensive fatty metamorphosis. Associated basal pulmonary densities were observed roentgenographically. Without the use of pancreatic extracts, except insulin, the liver and pulmonary pathologic changes apparently disappeared. A diet high in protein and insulin were the only therapeutic measures instituted. The etiologic relationships of these findings are discussed.

SIMPSON, S. LEONARD *(St. Mary's Hosp., London, W.2):* Some recent advances in endocrinology. Brit. M. J. *1*:725-30, April 5, 1952.

Experimental and biochemical research in endocrinology has thrown much light on clinical problems, but the clinician must not be overawed or fail to contribute his potentially invaluable observations and judgment. Work with pure growth hormone has shown its influence in wide clinical fields—namely, augmented weight, adiposity, diabetes mellitus, and lactation. The value, dangers, and limitations of cortisone and ACTH in endocrine and nonendocrine diseases are being clarified by experience. The problem of endocrine hyperfunction remains a serious challenge to endocrine therapeutics.

SMITH, A. N.; AND COCHRAN, J. B. *(Univ. of Glasgow, Glasgow, Scotland):* Islet-cell tumor of pancreas. Report of a case. Lancet *1*:289-93, February 9, 1952.

The authors report a case of islet-cell tumor of the pancreas, with successful surgical intervention. Various investigative studies, including administration of ACTH and cortisone, which were performed on this patient prior to operation are presented and the results discussed.

STADIE, WILLIAM C.; HAUGAARD, NIELS; AND VAUGHN, MARTHA *(Univ. of Pennsylvania):* The action of isotopic insulin bound to tissues. Science *115*:486, May 2, 1952.

The authors have previously reported that muscle, liver, adipose tissue, and lactating mammary glands of rats bind insulin and that the bound insulin exerts its customary effect on metabolism.

Isotopic insulin labeled with S^{35} and I^{131} was prepared to study the relation of biologic effect to mass of insulin. The experiments lead to the concept that a prerequisite for insulin action is a chemical binding on intact cellular elements. Contra-insulin effects of pituitary or adrenal hormones may either (a) inhibit the action of the bound insulin, or (b) inhibit the binding of insulin. In either case the metabolic activity of insulin would be decreased but by very different mechanisms. The distinction between these two possibilities is of fundamental importance in the problem of hormonal interaction.

STERN, JOHN J. *(St. Lukes-Memorial Hospital Center, Utica, N. Y.):* A new vasodilator in ophthalmology. Am. J. Ophth. *35*:187-90, February 1952.

Vasodilator therapy in the form of oral administration of priscoline tablets was used in three cases of angiospastic processes in the retina, in one of optic neuritis, and in one of neuroparalytic keratitis. Priscoline was used only in the form of 25 mg. tablets three or four times daily. The side effects (formication, hot flushes, chilliness) were never embarrassing; and the nausea, which is encountered occasionally because of the effect of the drug on the gastric mucosa, could be controlled with antacids. Because of these satisfactory results, the author recommends a trial with this preparation whenever angiospasm is considered to be responsible for similar processes.

UHRY, P.; DUCAS, P.; AND ELIACHAR, E. *(Paris):* Problem of abandoning strict diet for young children with diabetes mellitus; concept of "free diet" and its application to children. Semaine hôp. Paris *28*:1-38, January 2, 1952.

Free diet, in the sense of a diet that avoids overfeeding as its only restriction, is considered as desirable by the authors for the prevention of repeated symptoms of hypoglycemia and of ketosis. They believe that the mortality rate is no higher among diabetic patients on "free diet," and chronic infections no more numerous, than among those on a restricted diet.

WALAAS, EVA; AND WALAAS, OTTO *(Dept. of Biological Chemistry, Washington Univ. Sch. of Med., St. Louis):* Effect of insulin on rat diaphragm under anaerobic conditions. J. Biol. Chem. *195*:367-73, March 1952.

Insulin caused a significant stimulation of glucose uptake by rat diaphragm under strictly anaerobic conditions, but the effect was less than under aerobic conditions. Measurement of glucose uptake in oxygen preceded by anaerobiosis also resulted in a diminished response of the diaphragm to insulin. Insulin had no effect on the concentrations of phosphocreatine or ATP either aerobically or anaerobically and did not influence the rate of conversion of either glucose or glycogen to lactic acid. The authors attribute the effect of insulin on glucose uptake to a direct action on hexokinase.

WALLACE, DORIS M.: Diabetic detection. Am. J. M. Technol. *18*:39-44, January-February 1952.

The performance of laboratory tests for the detection of diabetes and the pre-diabetic state is discovered with emphasis on postprandial blood sugar determinations.

WEINSTEIN, PAUL: The significance of diabetic retinitis. Ophthalmologica *121*:353-56, June 1951 [Abstr. from Am. J. Ophth. *35*:296, February 1952].

The systemic finding in 30 cases of diabetic retinopathy are reported. There was a high incidence of high capillary fragility, of abnormalities of the electrocardiogram, and, in the cases of retinitis proliferans, of low creatinine clearance.

WELLS, C.; SHEPHERD, JOHN A.; AND GIBBON, NORMAN *(Dept. of Surgery, Univ. of Liverpool, Liverpool, England):* Pancreaticogastrostomy. Lancet *1*:588-89, March 22, 1952.

Three cases of pancreaticoduodenectomy, with implantation of the cut end of the pancreas into the stomach, are reported. This method is thought to be safer than pancreaticojejunostomy. All the operations appeared to be technically successful.

WHIPPLE, ALLEN O. *(Memorial Hosp., New York City):* Islet-cell tumors of the pancreas. Canad. M.A.J. *66*:334-42, April 1952.

In this Banting Memorial Lecture the history of hyperinsulism and islet-cell tumors is reviewed with side lights from the author's personal knowledge. Islet-cell tumors are predominantly functional, but both the benign and malignant in a few instances do not cause hyperinsulinism. The functional islet-cell tumors may be divided pathologically into four groups: benign adenomas (the most frequently found), questionably malignant adenomas, adenomatoses, and unquestionable carcinomas with metastatic spread. The benign adenomas may be multiple. For this reason, if one is found, the rest of the pancreas must be carefully searched for other tumors. In the order of frequency, benign adenomas are found in the tail, the head, and the body of the pancreas. To find these adenomas, especially those in the head, the pancreas must be mobilized by dividing its peritoneal attachments so that the firm nodular masses can be adequately palpated and detected. Benign adenomas, once removed, give immediate and permanent recovery from the hypoglycemic state. However, if the tumors have existed for long periods, permanent cerebral damage from repeated hypoglycemic attacks may result, even though the hyperinsulinism is cured. Recurrent hyperinsulinism as a result of recurrent or new islet-cell tumors is more likely to occur in patients with multiple adenomas, questionably malignant tumors, and adenomatosis found at the first operation.

WHITLEY, JAMES M.; AND ADAMS, THEODORE W. *(Portland, Ore.):* Diabetes and pregnancy. West. J. Surg. 60:98-107, March 1952.

The termination of a total of 79 pregnancies admitted to the Good Samaritan Hospital of Portland over a 10-year period is reviewed. There was an unusually high incidence of therapeutic abortions. Fifty pregnancies reached the period of viability (28 weeks). In this group there was a fetal mortality of 24 per cent. Closer cooperation between internist, obstetrician, and pediatrician is advocated. The series would seem to indicate that delivery at the 36th to the 38th week yields the best fetal salvage.

ZILLIACUS, H.; AND ROOS, B. E. *(Helsingfors, Finland):* Paper partition chromatography of sugars in pregnancy urine. Nordisk medicin, *47*:521-22, April 18, 1952.

Sugars were determined in the urine of 83 gravidae and in 1 case after delivery. Almén-Nylander's test for reducing substances was positive in 38 cases, but sugar caused the reduction in only 24 cases. Lactose was present in 17 cases; glucose appeared in 11; and both lactose and glucose were found in 4 cases.

ZIVIANI, NELSON *(Belo Horizonte, Brazil):* Hypoglycemias. O Hospital *41*:391-412, March 1952.

The author reviews current concepts of spontaneous and provoked hypoglycemias, including their etiological classification.

EDITORIALS

THE DIABETES DETECTION CAMPAIGN OF 1952

In its early years, the activities of the American Diabetes Association were directed almost exclusively to the medical profession. Its direct responsibilities to the diabetic population, and to the public in general, had been defined in the Constitution but it was not until 1948 that major steps were taken to fulfill its stated objectives in this field. It was in that year that the Association launched its magazine for diabetics, the A. D. A. FORECAST.

At the same time, a special committee was appointed "to increase public information about diabetes and to aid in the campaign to bring unknown diabetics under treatment through increasing the circulation of the A. D. A. FORECAST." It was thought that publicity might be more effective if promoted during that week in December, 1948 in which the American Medical Association held its midyear meeting. The Committee on Diabetes Week, later named the Committee on Diabetes Detection, was formed under the energetic leadership of Doctor Howard F. Root to stimulate nation-wide interest in diabetes. It secured the cooperation of local Diabetes Associations, county and state medical societies, and numerous individuals throughout the country. Although promotion of the magazine had been an initial consideration, this became merely a part of a broad objective to discover undiagnosed and neglected diabetics and to enable them to secure effective treatment. The Diabetes Detection Drive, initiated in Diabetes Week, became the opening phase of our year-round campaign.

Renewed efforts have been made annually. After a second year of distinctive achievement, Doctor Root turned over leadership to Doctor John A. Reed in 1950. Each year has seen the work of the Committee develop to a greater degree of effectiveness. The name was changed in 1951 to indicate that it is concerned with both diabetes detection and education. It is impossible to give an accurate appraisal of the results but unquestionably two benefits have been gained. Diabetics unaware of the disorder have been enabled to secure early diagnosis and to protect themselves from disability and even disaster. Known diabetics who have neglected treatmen have returned to medical supervision. In addition to the service rendered to individuals, there has been gained more widespread knowledge about diabetes.

The Campaign of 1952 will open with Diabetes Week, November 16-22. Plans have been made by Doctor Reed and his Committee to make even greater efforts than in the past. Information of other details has been placed in the hands of the leaders in each district and community. They are seeking workers among the medical profession and others interested in diabetes. The members of the American Diabetes Association have a special responsibility to make the campaign a success. This is a challenge and an opportunity to further the welfare of diabetics.

INTERNATIONAL MEETINGS

Since the war, there has been an increase in the number of international medical and scientific organizations. In the past summer, for example, there took place no less than four such assemblies or conferences of interest to those concerned with diabetes.

The International Diabetes Federation met in The Netherlands, July 7-12. It represented the first Congress of the Federation, formed three years ago to coordinate the activities of the various national associations which have developed to promote the welfare of diabetics. The program, presented partly in English and partly in French, included scientific sessions and also meetings at which physicians and lay workers discussed matters of

particular interest to patients and laymen. In addition to the exchange of information in the formal program, the opportunity for personal acquaintance of individuals with a common interest in diabetes was particularly valuable.

The International Dietetic Congress met in Amsterdam concurrently, and on one day joint meetings were held. The advantage of a close relationship between dietitians and physicians in the management of diabetes is recognized locally and internationally.

The Ciba Foundation conducted a conference in London from June 30 to July 3. This institution was formed by the Ciba Company in 1947 for the promotion of international cooperation in medical and chemical research. One of its functions is to bring together groups of scientists active in similar fields of research. Charles H. Best was chairman of the recent conference which dealt with endocrine inter-relationships in carbohydrate metabolism. It was attended by approximate forty-five scientists from Europe and North America.

A symposium on experimental diabetes and its relationship to the clinical disease was presented at Leyden, The Netherlands, during the four-day period immediately following the Congres of the International Diabetes Federation. It was organized by the Council for the Coordination of International Congresses of Medical Sciences, (now named The Council of International Organizations of Medical Sciences), established under the joint auspices of the United Nations Educational, Scientific, and Cultural Organization (UNESCO) and the World Health Organization. F. G. Young, of Cambridge, was chairman.

The papers and the informal discsusions presented at the London and Leyden conferences will be published in book form. The papers presented at the International Diabetes Congress will also be published in full or in abstract form. As a result of these four international meetings, there will thus be enrichment of the literature relating to diabetes.

FAT AND BODY COMPOSITION

Within recent years, as a result of the introduction of new technics, there has been a shift in emphasis from metabolic balance studies to investigations of the total composition of the body. From such studies we are beginning to accumulate knowledge of the fat content of the normal body and the distortions in this component which occur in diseased states.

Brozek and Keys[1] have investigated the total fat content of normal men by means of the measurement of the specific gravity of the body. With subjects whose body weights were within 10 per cent of the standard weight, they found that the specific gravity decreased with age. Thus, in the process of aging, a shift occurs in the partition of the body components with an increase in the fat content. This can be detected in an increase in skin folds and a decrease in the difference between the circumference of the chest and abdomen.

In two recent communications from a group at the Harvard Medical School and the Peter Bent Brigham Hospital[2, 3] the fat content of the body has been determined indirectly through the estimation of the total body water content by the deuterium oxide dilution technique. These studies reveal significant variations in the total water content of the body throughout the life span. There is a trend toward high values at birth and in infancy, with a fall to the adult level at about 4 years of age where it remains until the fourth decade followed by a further decline in older age. At about the age of 16 years, a significant sex difference appears; the male body has a 17 per cent greater water content than the female body.

Since there is an inverse relationship between the fractions of body water and body fat, it is apparent again that the fat component of the body increases with age, and after puberty is greater in the female than in the male body. At any given age, the normal partition of water and fat may be markedly affected by diseased states and the degree of distortion may determine the toleration, on the one hand, to dehydration and, on the other hand, to semi-starvation.

Although the estimation of total body fat by the measurement of the specific gravity has revealed important basic information, it is not feasible for clinical use. However, the determination of the total body water by the deuterium oxide dilution technic eventually may have a clinical application.

ROSEMARY MURPHY, M.D.

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[1] Brozek, J. and A. Keys: Age changes of total body fat in normal adult men. Federation Proc. *11*:18-19, March 1952.

[2] Edelman, I. S. et al: Further observations on total body water I. Normal values throughout the life span. Surg., Gynec. & Obst. *95*:1-12, July 1952.

[3] Moore, F. D. et al: Further observations on total body water II. Changes of body composition in disease. Surg., Gynec. & Obst. *95*:155-180, August 1952.

Paul Langerhans 1847-1888

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Time and history weave patterns with seemingly unrelated facts, as the weaver of a Persian rug blends varied threads through his loom to produce a design of ageless beauty. So it is with the facts of medical knowledge. Gathered and contributed by many workers, they may seem inconclusive or even insignificant at the time of their publication. But when they have been properly assembled and wisely interpreted, they, too, make patterns — of knowledge, if not of beauty. Such are the materials of scientific achievement in medical history.

Today, every medical student the world over knows of the islets of Langerhans. Their textbooks tell them that the islets of Langerhans are cellular structures within the pancreas, and that these structures have an important relationship to diabetes. But very few know anything about Paul Langerhans; who he was, when and where he lived, and how he made his discoveries. The name of Langerhans has already endured in medicine for 85 years, and it will undoubtedly be preserved in medical annals for centuries to come.

The most complete source of biographical information on Paul Langerhans is an essay by Morrison,[1] whose interest in Langerhans was motivated by a search for outstanding contribution to medicine made by men still in their undergraduate years. This was an interesting approach to the biography of a man, and it should be of particular interest to members of the American Diabetes Association.

Paul Langerhans, working in Virchow's laboratory at the Berlin Pathological Institute, began the study of anatomy of the pancreas in 1867 and reported his findings in 1869. A similar instance of medical discovery by an undergraduate student of medicine occurred on this continent within our own lifetime. At the University of Toronto, a graduate student in physiology while still an undergraduate student of medicine, working with Dr. Frederick Banting in 1921-1922 became the co-discoverer of insulin. His name is Charles Best. Never underestimate the powers of a medical student! That is something for oldsters to keep in mind, as we tread the corridors of our schools of medicine.

Paul Langerhans was born in Berlin on July 25, 1847. His father, Dr. Paul Langerhans, was a physician; his mother (née Keibel) was a cousin of Franz Keibel, the eminent histologist. One brother, Robert Langerhans, an assistant to Virchow, was professor of pathology and another brother, Richard Langerhans, was an honored practitioner of medicine in Berlin. As a student in Jena, Paul was the pupil of Ernst Haeckel, his "adored teacher." Later in Berlin, Paul was influenced particularly by Julius Cohnheim and Rudolf Virchow, with both of whom he had developed close friendships. In all of this we see what can happen when good seed is planted in good soil, and when a good inheritance finds a good environment.

In the time of Langerhans, Claude Bernard had already demonstrated that the pancreas played an important role in the digestion and assimilation of carbohydrate, protein and fat. At that time the pancreas was simply described as a racemose gland, containing a mass of infiltrating fat. The adjective racemose was applied in a purely morphologic sense, intended to convey the picture of a raceme plant in which the flowers are attached to short stalks which spring from the main stem, like the flowers of the lily-of-the-valley. This description is quite applicable to the appearance of the glands of external secretion of the pancreas, but unfortunately it revealed little more than that.

Of the existing knowledge pertaining to physiology of the pancreas at that time, Langerhans said, "There is indeed hardly another organ in which there is such glaring contrast between the brilliant results of physiologic research and the complete darkness in the realm of anatomic knowledge. Practically all that receives any thorough consideration from the anatomic point of view is the relationship of this gland to the peritoneum or whether the opening of this or that excretory duct is at a higher or lower level."

Langerhans' early observations were made on the rabbit; later he studied the salamander, guinea pig, dog, cat, pigeon, snake, frog, hen, as well as man. He studied the

fresh and fixed state of pancreatic tissue, fragmenting the tissues into minute particles for microscopic study. After maceration of pancreatic tissue he differentiated nine different types of cells. Of these, one type in particular puzzled him greatly. "This cell," he said, "is a small irregularly polygonal structure, with brilliant cytoplasm; free of any granules with distinct round nuclei of moderate size. These cells lie together in considerable numbers, diffusely scattered in the parenchyma of the gland." Langerhans said he did not know the nature of the cells, and he felt that the best that he could do at the time was simply to call attention to them as deserving of serious study.

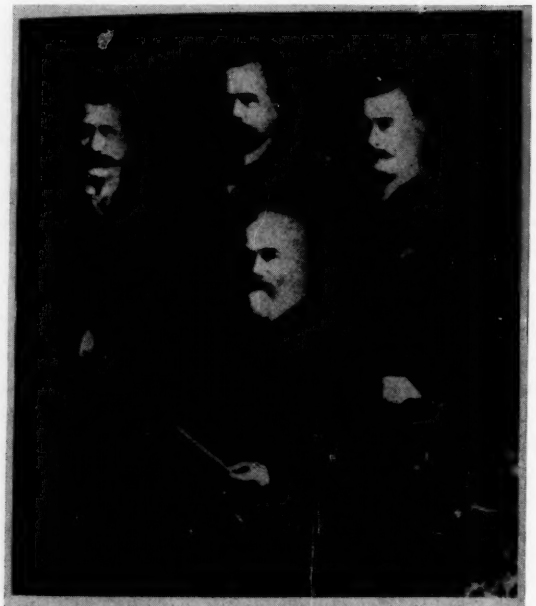
Later, observers found these cells present in the pancreas of all vertebrates. Twenty-four years later, Laguesse, a French histologist, noted these clusters of cells in the human pancreas, identified them as the ones already described by Langerhans, and called them "the islets of Langerhans." Laguesse expressed his opinion that these cells were the seat of an internal secretion of the pancreas.

Between the time of Langerhans' observations in 1869 and those of Laguesse in 1893 Kühne and Lea in 1882 demonstrated an intimate relationship between these cells and the capillaries and nerves of the pancreas. And then Dogiel in 1893 further showed that there was no connection between these cells and the duct system of the pancreas.

During the year 1870 Paul Langerhans travelled through Northern Africa and Asia Minor. He wrote letters home to Virchow, commenting on leprosy, on the skull measurements of bedouin and fellahin, and he commented in general on the backward state of medicine in the near east, as he saw it in the city of Jerusalem and elsewhere. Toward the end of that year, Langerhans returned to Germany. The Franco-Prussian War was raging, and he took clinical service in a Berlin hospital and ambulance service at the front.

After the war he worked with the famous Carl Crede, director of the obstetric and gynecologic wards at the Charité Hospital in Leipsig. Crede's name became widely known in connection with silver ointment. There Langerhans engaged in research and teaching for four years; his publications on the histology of the heart, genital organs and other subjects appeared in Virchow's *Archives*.

Following that period he was elected to full professorship. Unfortunately he had to give up this position because of active tuberculosis. To regain his health he moved to the island of Madeira, hoping for a cure. There he continued his research in zoology. He recovered sufficiently while on Madeira to resume the practice of medicine.



Sitting: Dr. PAUL LANGERHANS, senior
Standing: Middle—PAUL LANGERHANS
Left—Sanitats-Rat Dr. RICHARD LANGERHANS
Right—Professor Dr. ROBERT LANGERHANS
September 10, 1884

In 1885 he married Margarethe Ebart with whom, as he said, he enjoyed three years of complete happiness. In 1888, following a systemic infection, he developed a serious kidney complication and on July 20th of that year, at the age of 41, he died—and was buried in Madeira. Thus ended the career of a young man who had made a brilliant and valuable contribution to medicine and to human welfare.

As we know, medical discovery in any field does not begin or end with one man. In the year after Paul Langerhans' death, von Mering and Minkowski reported the appearance of diabetes after experimental pancreatectomy. In 1901 the paper by Opie in which he described changes in the islets of Langerhans furnished evidence of the association of these structures with carbohydrate metabolism.[2] In a personal letter to me written February 22, 1952, Opie made the following interesting comment: "When I was a second-year medical student in pathology, I found a body queer to me in a cross section of the pancreas and asked Dr. Welch what it was. Welch told me that these structures had been described by Langerhans in an inaugural dissertation,[3] and added; 'Find out all you can about them."Here was another medical student at work! Today we have a full appreciation of the value of Opie's contribution to the subject. His book on the

pancreas was a byword in the medical world for many decades.

One of the anatomists to make classical contributions concerning the structure of the pancreas was our contemporary, Professor Richard R. Bensley. Bensley clarified to a large extent the relation of the islets of Langerhans to the ducts of the pancreas, the independence of the islets from acinar tissue, and the cell types in the islets. It has been said that Banting expressed great appreciation of the work described in Bensley's Harvey Lecture on the pancreas. In personal letters recently received from Russell M. Wilder and from Charles H. Best, both paid further tribute to Bensley. As I write, Professor Bensley has reached his eighty-fourth year, so let us honor the octogenarians in medicine as well as the medical students.

There are many more links in the chain of medical history that binds the period of Langerhans and the period of Best. Only a few of them could be mentioned in this brief sketch of the life of Paul Langerhans, but these few that I have noted are basic. They will stand for all time, linking the past with the present, and the future that is to come.

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BOOK REVIEW

DIABETES AND PREGNANCY. *Blood Sugar of Newborn Infants during Fasting and Glucose Administration.* By Jorgen Pedersen, M.D. No Price indicated. Paper. Pp. 230. Illustrated. Danish Science Press Ltd. Copenhagen, 1952.

This monograph presents a detailed summary of extensive and well-planned studies done in a lying-in hospital, Copenhagen, Denmark. It deals with carbohydrate metabolism during pregnancy in diabetic and nondiabetic women and with carbohydrate metabolism in their infants. The first chapter reviews current knowledge of carbohydrate metabolism in mammalian fetuses and newborn young. Subsequent chapters present an extensive review of previous investigations regarding carbohydrate metabolism in infants of nondiabetic and diabetic mothers, maternal blood sugar and blood sugar of infants of diabetic and nondiabetic mothers at birth, in the first 24 hours of life and during later neonatal periods, and to theories previously advanced regarding homeostatic mechanisms of control.

The writer's own investigations are summarized in chapters dealing with blood sugar levels in the mothers, with regard to duration and treatment of their diabetes (including complications), blood sugar levels in the infants of diabetic and nondiabetic mothers in the first 24 hours and later neonatal periods, in relation to sex, birth, weight, gestation time, maternal anesthesia, cyanosis at birth and after, maternal insulin dosage, responses to oral glucose tolerance tests.

Some salient findings emphasized in the author's summary are as follows: 1. During the first 24 hours of life, the course of the blood sugar curve was, in general, the same in infants of diabetic and nondiabetic mothers when the infants were kept under standard conditions; 2. Infants of diabetic as well as nondiabetic mothers withstood fasting 24 hours without exhibiting any constant decrease in blood sugar; 3. During the first 24 hours, there was a negative correlation between the mean blood sugar of the infant and the maternal mean blood sugar during the latter months of pregnancy; 4. The infants blood sugar varied also with the birth weight; this correlation being negative among the infants of diabetic and positive among those of nondiabetic mothers; 5. The mean blood sugar was subject to wide variations, in infants of both diabetic and nondiabetic mothers; 6. No correlation was found between symptons, such as cyanosis during the neonatal period and the infants' blood sugar; 7. Oral glucose tolerance tests during the first eight days of life were variable in both infants of diabetic and of nondiabetic mothers.

In a final chapter the writer discusses hypotheses regarding blood sugar regulations in newborn infants, including the homeostatic liver mechanism, without stating very definite conclusions but supporting as plausible the old hypothesis that maternal hyperglycemia in the pregnant diabetic may lead to fetal islet cell hypertrophy. An excellent bibliography includes 188 references.

Recent Data On DIABETES

Herbert H. Marks

CHAIRMAN, COMMITTEE ON STATISTICS

DIABETES DEATHS AND DEATH RATES, 1950-1951

The death rate from diabetes in the United States in 1951 was slightly lower than in 1950. This small reduction is observed both in the national figures, based upon a 10 per cent sample of death certificates collected by the National Office of Vital Statistics, and in the experience among Industrial policyholders of the Metropolitan Life Insurance Company. The downward trend is seen also in the figures for most of the local areas in the United States included in Table 1. The death rates in the two Canadian cities were higher in 1951 than in 1950.

For England and Wales, the death rate in 1951 was virtually identical with that for 1950. This is in contrast with the situation earlier in the year when the rate was well above that for 1950, due principally to the severe influenza epidemic in the winter of 1951. The mortality in the last quarter of the year was extremely low. These findings apply separately to males and females. In the Administrative County of London, the recorded number of deaths from diabetes sharply increased in 1951 over 1950. This may reflect the increasing importance of London as a hospital center for treatment of diabetes.

In the first quarter of 1952 the death rate from diabetes in the United States shows an appreciable fall from the same period of 1951. National data, based upon the 10 per cent sample of death certificates, indicate a reduction of 8 per cent. The decline in the rate among Industrial policyholders of the Metropolitan Life Insurance Company was more than twice as large. To some degree this decline reflects the decreased prevalence of respiratory disease in the first quarter of this year as compared with last year.

The mortality statistics for diabetes in local areas, in Table 1, as well as the regional figures given in Table 2, show no consistent trends for the first quarter of 1952 as compared with the same period of 1951. These figures for local areas, however, are more subject to chance fluctuations than are the national figures.

In England and Wales, also, the death rate from diabetes in the first quarter of 1952 is sharply down. The reduction from a year ago is nearly 25 per cent. Both sexes show a decrease in mortality from the disease but the decline is greater for the females. A great part of the reduction reflects favorable health conditions in the

country last winter. In contrast, the winter of 1951 was marked by the epidemic, already referred to, which raised both the general mortality and the mortality among persons with chronic diseases. The death rate from diabetes in the first quarter of 1952 is lower than that recorded in any similar period since 1948. Later data for London covering the first half of the year show a moderate decline in the number of deaths from the disease.

TABLE 1 RECENT DATA ON DIABETES MORTALITY

Deaths and Death Rates—1950 and 1951

Area	Death Rates per 100,000		Number of Deaths	
	1951	1950	1951	1950
United States (10% sample)	16.5	16.6	2528	2501
Metropolitan Life Ins. Co.				
Industrial Policyholders	15.2	15.5	2847	2952
New York State	20.1	20.6	3024	3058
New York City	17.8	20.0	1416	1584
Maryland	20.0	17.6	482	415
Baltimore	22.6	19.0	216	180
Boston	26.2	29.0	210	233
Philadelphia	24.1	25.0	504	516
Toronto	17.3	15.6	113	104
Montreal, Resident	16.7	16.4	171	174
London (Administrative County)			322	266
England and Wales				
Total	8.5	8.4	3706	3684
Males	5.8	5.8	1221	1221
Females	10.9	10.9	2485	2463

Deaths and Death Rates—January-March 1951 and 1952

Area	Death Rates per 100,000		Number of Deaths	
	1952	1951	1952	1951
United States (10% sample)	16.6	18.1	634	682
Metropolitan Life Ins. Co.				
Industrial Policyholders	13.7	17.0	631	797
New York State	21.6	22.2	820	824
New York City	20.7	21.1	416	422
Maryland	19.8	24.9	121	148
Baltimore	26.1	22.2	62	52
Boston, Resident	30.8	27.8	62	56
Philadelphia	31.2	26.7	164	138
Toronto	12.9	22.3	21	36
Montreal, Resident	18.6	20.8	48	53
London (Administrative County)				
(First 26 weeks)			156	169
England and Wales				
Total	8.8	11.6	955	1252
Males	6.2	7.8	324	406
Females	11.2	15.1	631	846

Note: Rates for the states and cities based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in Current Mortality Analysis, a monthly report of the National Office of Vital Statistics of the U.S. Public Health Service.

TABLE 2 Number of Deaths and Death Rates for Diabetes in Geographic Division; United States Reporting Area for the 10-per cent Sample; January-March 1950, 1951 and 1952

Note: These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the "Current Mortality Analysis."

Source: Data furnished by National Office of Vital Statistics of the U.S. Public Health Service.

Geographic Division	Death Rates per 100,000*			Number of Deaths		
	1952	1951	1950	1952	1951	1950
U.S. reporting area	16.6	18.1	18.5	634	682	685
New England	20.8	30.1	23.3	48	70	54
Middle Atlantic	22.0	18.1	23.7	169	136	179
East North Central	19.2	24.9	23.2	149	189	175
West North Central	19.0	19.7	21.0	68	69	74
South Atlantic	12.9	15.1	15.2	70	80	76
East South Central	11.6	9.8	10.7	34	28	30
West South Central	10.2	11.6	13.7	38	42	49
Mountain	15.4	12.6	6.9	20	16	8
Pacific	11.1	14.4	11.2	38	52	40

*Excludes armed forces overseas.

DIABETES MORTALITY AMONG METROPOLITAN LIFE INDUSTRIAL POLICYHOLDERS, 1951

The latest annual figures for diabetes mortality by sex, color and age, based upon the mortality experience among Industrial policyholders of the Metropolitan Life Insurance Company is presented in Table 3. Of particular interest is the fact that among colored persons in the urban wage-earning population, which constitutes the major part of this insurance experience, the age-adjusted death rate, for all ages 1 to 74, is higher than among white persons. This is true for both males and females. For males the excess of the colored over the white rate is 18 per cent, and for females, 32 per cent.

TABLE 3 Death Rates per 100,000 from Diabetes Mellitus by Color, Sex, and Age Periods. Metropolitan Life Insurance Company, Industrial Department, Weekly and Monthly Combined, 1951

Age Period (Years)	Total Persons	White		Colored	
		Males	Females	Males	Females
1 to 74*	9.2	6.8	11.1	8.0	14.7
1 - 4	.4	.5	.3	—	—
5 - 14	.5	.2	.8	—	.7
15 - 24	1.2	.9	1.3	1.8	1.7
25 - 34	1.9	1.7	1.7	2.3	4.1
35 - 44	4.1	5.3	1.9	7.9	10.3
45 - 54	14.6	11.1	12.0	22.3	33.4
55 - 64	52.4	34.2	62.4	29.2	70.6
65 - 74	120.4	71.0	149.1	67.9	136.7

*Standardized for age, Standard Million of England and Wales, 1901

DIABETES MORTALITY IN THE UNITED STATES, BY AGE GROUPS, 1949-1950

For the general population, preliminary data on diabetes mortality by age are now available for the year 1950. These are shown in Table 4. There are no marked changes from the year 1949 in the age specific death rates.

TABLE 4 Number of Deaths and Death Rates per 100,000 from Diabetes Mellitus by Age. United States, 1949 and 1950 (Excludes Armed Forces Overseas)

Age Periods Years	Death Rates		Deaths	
	1950*	1949	1950*	1949
All Ages	16.6	16.9	25,076	25,089
Under 1	1.6	.3	52	10
1 - 14	.3	.4	120	162
15 - 24	1.0	1.4	220	304
25 - 34	2.2	2.1	511	484
35 - 44	4.2	4.0	882	821
45 - 54	12.4	13.4	2,165	2,314
55 - 64	45.1	45.6	6,146	6,096
65 - 74	111.1	113.7	8,763	8,736
75 - 84	167.4	170.6	5,413	5,334
85 and over	162.2	176.4	782	813
Not stated			22	15

*Estimated

Source: National Office of Vital Statistics

DIABETES DEATH RATES IN THE UNITED STATES BY AGE, COLOR AND SEX, 1949

Table 5 presents final national figures by color, sex and age for 1949, the first year in which the Sixth Revision of the International List came into use in this country. The statistics, given by detailed quinquennial age groups, show that even with the Sixth Revision there is a charac-

TABLE 5 Number of Deaths and Death Rate per 100,000 from Diabetes Mellitus by Age, Race and Sex. United States, 1949 (Excludes Armed Forces Overseas)

Age	Death Rate					Deaths				
		White		Non-White			White		Non-White	
	Total	Male	Female	Male	Female	Total	Male	Female	Male	Female
All Ages	16.9	13.2	21.2	9.3	18.6	25089	8717	14158	714	1500
Under 1	.3	.3	.4	—	—	10	5	5	—	—
1 - 4	.3	.3	.3	.1	.4	40	19	17	1	3
5 - 9	.3	.3	.4	.1	.2	43	15	25	1	2
10 - 14	.7	.6	.8	.9	.9	79	28	37	7	7
15 - 19	1.2	.9	1.3	2.5	2.5	131	40	58	16	17
20 - 24	1.5	1.2	1.5	2.1	2.9	173	61	78	14	20
25 - 29	1.9	1.5	1.8	4.5	3.4	228	78	99	28	23
30 - 34	2.3	2.5	1.5	3.9	5.0	256	125	78	21	32
35 - 39	3.1	3.2	2.1	4.7	9.3	339	154	106	24	55
40 - 44	4.9	4.0	3.7	7.8	20.6	482	176	169	35	102
45 - 49	9.0	7.2	7.4	14.5	33.2	816	291	305	62	158
50 - 54	18.4	14.5	18.2	21.4	56.6	1498	538	684	74	202
55 - 59	34.0	24.2	40.6	31.3	73.4	2493	819	1380	87	207
60 - 64	59.6	41.3	76.2	41.1	102.5	3603	1157	2151	88	207
65 - 69	96.9	69.2	123.2	61.7	136.4	4334	1408	2640	95	191
70 - 74	137.1	103.9	170.9	78.8	134.7	4402	1476	2708	82	136
75 - 79	160.0	139.3	185.9	67.7	116.7	3337	1247	1969	44	77
80 - 84	191.7	177.6	221.2	51.4	83.3	1997	776	1168	18	35
85 & over	176.4	174.1	209.3	58.3	58.3	813	303	475	14	21
Not Stated						15	1	6	3	5

Source: Federal Security Agency, Public Health Service, National Office of Vital Statistics. Special Reports—National Summaries, Vol. 36, No. 14, March 21, 1952

teristic rise in the death rate from diabetes with advancing age in each color and sex group, although this rise is less pronounced than in statistics based upon the Fifth Revision of the list.* In "A" the peak of the death rates from diabetes is reached in white persons after age 80, and in colored persons about 10 to 15 years earlier. The death rates for women are still well above those recorded for men at ages past 45 when diabetes is a significant factor in the total death rate.

*Details on the effects of the Sixth Revision of the International List of Diseases, Injuries and Causes of Death on the recorded mortality from diabetes are given in (1) *Proceedings of the American Diabetes Association*, Volume 9, 1949, pp. 347-361, and (2) *Diabetes*, Volume 1, No. 3, May-June 1952, pp. 205-217.

ENGLISH HOSPITAL DIABETES IN-PATIENT DISCHARGES, 1949

Statistics of morbidity from specific diseases are relatively scanty. A new addition to the sparse literature in the field is the monograph on Hospital Morbidity Statistics, which gives preliminary data on in-patient discharges for a number of English hospitals. The report is based on the trial tabulation of the summary forms used in the investigation, for the first six months of 1949 that had reached the General Register Office by April 1, 1950. Table 6 shows the relative volume of diabetes as a cause of hospital admission, by sex and age. Thus, in the aggregate, diabetes was the cause of admission in 0.8 per cent of the total cases discharged. It should be distinctly understood that this figure does not cover all the diabetics but merely those in which the diabetes was the primary cause of admission. Unfortunately, the report does not give any information with regard to diabetics who were admitted for other reasons.

The proportion of cases admitted for diabetes was slightly greater among males than among females, although in absolute frequency the females outnumber the males both for all causes of admission and for diabetes. Also, both absolutely and relatively, the frequency of diabetes as a cause of admission was distinctly greater in females at ages past 55.

Certain other aspects of this study are of interest. The length of hospital residence was distinctly greater for those admitted for diabetes than for all patients. Thus, the mean number of bed-days in the hospital was 23.5 for males admitted for diabetes as compared with 19.2 days for all cases. For females the figures were 22.7 and 17.7 days, respectively. Accordingly, for diabetics the proportion of bed-days to the total was appreciably greater than the corresponding proportion of discharges. For males the bed-days for cases admitted for diabetes constituted 1.1 per cent of the total, whereas, the cases constituted 0.9 per cent of the total discharged. For females the figures are 1.0 per cent and 0.8 per cent respectively.

The proportion of diabetics who died in the hospital was comparatively high. For males the figure was 4 per cent, and for females, 7 per cent. No details are given on the causes of death of these diabetitcs.

TABLE 6 Number of In-Patient Discharges Admitted to Hospitals for Diabetes and Per cent These Are of All Discharges, by Sex and Age. Sample of Returns to Hospital Morbidity Enquiry (England and Wales) for the First Six Months of 1949

Age Period Years	Total*			Diabetes			Per cent Diabetes of Total		
	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female
All Ages	130,938	53,786	77,152	1,086	469	617	.8	.9	.3
Under 1	3,121	1,898	1,223	—	—	—	—	—	.3
1 - 4	7,456	4,244	3,212	13	7	6	.2	.2	.5
5 - 14	15,108	8,173	6,935	77	31	46	.5	.4	.8
15 - 24	17,570	4,891	12,679	100	56	44	.6	1.1	2.4
25 - 34	23,071	5,728	17,343	100	51	49	.4	.9	2.9
35 - 44	19,860	7,054	12,806	120	62	58	.6	.9	2.3
45 - 54	17,151	7,881	9,270	145	70	75	.8	.9	.5
55 - 64	13,963	7,216	6,747	253	94	159	1.8	1.3	.8
65 - 74	9,530	4,745	4,785	216	77	139	2.3	1.6	—
75 and over	3,421	1,705	1,716	56	17	39	1.6	1.0	.2
Not stated	687	251	436	6	4	2	.9	1.6	.7

*Excludes Live Births and other special admissions.

Source: Hospital Morbidity Statistics. A Preliminary Study of In-Patient Discharges. Studies on Medical and Population Subjects No. 4. General Register Office, London, 1951.

ORGANIZATION SECTION

The First Congress of the International Diabetes Federation

The First Congress of the International Diabetes Federation was held in Leyden, The Netherlands, July 7-12 1952, with many American participants present.

The Congress was opened by Professor J. D. Boks, Dean of the University of Leyden. The first speaker for the International Diabetes Federation was Dr. Elliott P. Joslin, Honorary President of the American Diabetes Association. Dr. Charles H. Best, Past President of the American Diabetes Association, presented the inaugural address, and Dr. R. D. Lawrence, President of The Diabetic Association of Great Britain, and the current President of the International Diabetes Federation, also spoke. Both Drs. Joslin and Best are Honorary Presidents of the Federation.

Fifteen countries were represented at this First Congress, and there was a total registration of 241 delegates, of which thirty were from the United States. Many registrants were accompanied by their wives and families, so that about 400 persons participated in sessions. The American Diabetes Association is not a member of the International Diabetes Federation, but it was represented officially at the Congress by its President, Frank N. Allan, M.D., and its Executive Director, Mr. J. Richard Connelly.

Although the Federation is a young organization, its First Congress was exceedingly well organized and carefully scheduled. Great credit for the excellent arrangements is due to its Secretary-Treasurer, Dr. F. Gerritzen, Mrs. Gerritzen and the Federation's Executive Secretary, Mr. Pierre Duys.

Scientific sessions occupied five and a half days and were pleasantly interspersed with social activities and sight-seeing tours. Meetings of lay representatives to cover social and economic aspects of diabetes were conducted concurrently with the scientific sessions on two days.

The gracious hospitality of the Dutch, including members of the Nederlandse Vereniging van Suikerzieken and the faculty of the University of Leyden, came to a climax at the banquet of the Congress, which was held on Thursday evening, July 10, at the famous resort hotel, the Huis-ter-Duin, at Noordwijk.

Among its organizational accomplishments, the following Constitution Committee was appointed: Maître Maurice Paz, France, Chairman; Sir Henry Digby-Beste, England; Dr. F. Gerritzen, The Netherlands; and Mr. J. Richard Connelly, United States. This committee drafted a new Constitution and By-Laws and plans are being made to submit it to the Associations of the International Diabetes Federation for ratification.

Through the courtesy of Mr. Pierre Duys, Executive Secretary of the IDF, we are able to quote Article III of this draft Constitution, outlining the aims of the IDF:

"The objectives of this Federation are to acquire and disseminate useful and accurate information regarding diabetes mellitus and to undertake such activities as will improve the individual, physical, social and economic well-being of persons having that disorder.

"To these ends it is the purpose of the Federation to promote the free exchange of knowledge with respect to diabetes mellitus; to improve the standards of treatment of diabetes mellitus; to promote medical and other related scientific research, as well as statistical, social and economic investigation pertaining to diabetes mellitus; to develop educational methods designed to give diabetic patients a better understanding of their disease; to educate the general public in the early recognition of diabetes mellitus and in the importance of medical supervision of its treatment; and to encourage the creation of national diabetes associations, which it is believed will assist in fulfilling the objectives of the Federation.

"Further, it is the aim of the Federation to take all such measures within its ability, necessary to achieve the above objectives, and in particular to organize congresses and meetings pertaining to the scientific and medical aspects of diabetes mellitus, as well as the social and economic problems of that disorder."

The various national Associations affiliated with the IDF are:

Australia	The Diabetic Association of Australia G.P.O. Box 4746, Sydney, N.S.W.
Belgium	Association belge pour la defense des intérets des Diabétiques 451, Avenue Louise, Brussels
Canada	The Diabetic Association of Ontario 111, Avenue Road, Toronto
Denmark	Landsforeningen for Sukkersyge Klingenberg 15, Odense
Finland	Sokeritautisten Yhdistys Meritullinkatu 5 B 19, Helsinki
France	Association francaise des Diabétiques 83, Boulevard de l'Hopital, Paris XIIIe
Germany	Deutscher Diabetiker Bund e.V. Strohberg 103, Stuttgart-Süd
Great Britain	The Diabetic Association 152, Harley Street, London, W. 1
Italy	Associazione Italiana per la difesa degli interessi dei Diabetici Via Bersilia 2, Rome
Netherlands	Nederlandse Vereniging van Suikerzieken Prinsegracht 33, the Hague
Norway	Norges Landsforbund for Sukkersyke P. O. Box 1456, Oslo
Portugal	Associacao Protectora dos Diabeticaos Pobres Rua de Victor Cordon 12-2, Lisbon
Spain	c/o Prof. Dr. C. Jiménez Diaz General Mola 9, Madrid
Sweden	Riksforbundet for Sockersjuka Rosengatan 14, Sundbyberg (Stockholm)
Uruguay	Associacion de Diabéticos del Uruguay Calle Soriano 1215, Montevideo

During the meeting of the General Council of the IDF, the following members of the Board were elected unanimously:

Honorary Presidents

Elliott P. Joslin, M.D., Boston, Massachusetts
Charles H. Best, M.D., Toronto Canada

EXECUTIVE BOARD

President

R. D. Lawrence, M.D., London, England

Vice-Presidents

Prof. Dr. J. P. Hoet, Louvain, Belgium
Me. Maurice Paz, Paris, France
Howard F. Root, M.D., Boston, Massachusetts

Secretary-Treasurer

F. Gerritzen, M.D., Wassenaar, Holland

Executive Secretary

Mr. Pierre Duys, c/o Nederlandse Vereniging van Suikerzieken, Prinsegracht 33, The Hague

The Beginning of The Diabetic Association in England

R. D. Lawrence, M.D.
PRESIDENT, THE DIABETIC ASSOCIATION, LONDON

"The love of money is the root of all evil" saith the prophet. But the need for money in a good cause can be a powerful stimulus; indeed it led to the beginning of *The* Diabetic Association in 1933. I make no apology for this title as it was the first and only Association then, although such organizations have now spread everywhere. Indeed it was the first time that a body of sufferers from any disease banded themselves together for mutual help.

I hope I may be forgiven for being personal in this story. In London, as elsewhere, insulin had produced by 1931 a vital snowballing of living diabetics. At King's College Hospital, I myself had been given charge of them in our small biochemical laboratory. They occupied all odd seats so extensively as to threaten the extinction of Bunsen burners and all other routine work. Our voluntary hospital had no money to spare for equipping a new department, so I started to raise money from some of my rich and grateful diabetic patients for a new diabetic department. Amongst these I approached the great writer, H. G. Wells, who, not feeling so affluent in his contribution as I expected, offered to write a letter of appeal to *The Times*. This is interesting in being the first public intimation of the profound debt diabetics felt for the progress of treatment and the discovery of insulin. I shall quote parts of Wells' letter of appeal.

THE SELECT COMPANY OF DIABETICS

"Sir, — May I make an appeal through your columns, not to all your readers, but to that select percentage of them who are diabetic and who 12 years ago would have been "suffering from diabetes"?

"Some hundreds of thousands of people to-day who have this physiological idiosyncrasy are living active and happy lives thanks either to a scientifically regulated dietary or to the use of insulin. Many of them — many of us, to be more personal—would either be dying slowly and uncomfortably or be already dead if it were not for the work of a small group of experimentalists and practitioners who have brought this particular maladjustment under control, and none of us can feel anything but the liveliest gratitude for that work.

"An opportunity occurs for expressing this gratitude in a very direct and effective fashion. We can contribute to the research that is still perfecting the very precise and beautiful treatment by which we have been restored to normality, and we can help to extend its benefits to many fellow diabetics not so well off as ourselves who would otherwise be obliged to cease work and so cease to be self-supporting.

"I suggest that it would be a becoming thing of the elect class of grateful diabetics to whom I appeal to tax themselves for the benefit of our cult. If 40 of us would put up £20 each the thing would be done. When I think of the relief our treatment has given us and the real invigoration, the bracing effect, of its clear and rational discipline, £20 seems to me a small sum. Indeed, as I think the matter over I am a little surprised we have not already formed a Diabetic Association, to watch over and extend this most benign branch of medical science to which we owe our lives. I will not, however, let my imagination run on to an Annual Dinner for Old Diabetics, or to the organized propaganda of our simple requirements among cooks and hotel and restaurant proprietors. The immediate business in hand is to raise that £800, and I shall be very glad to hear from all my fellow diabetics who are

willing to assist in any measure in raising this not very considerable sum. The participation of friendly non-diabetics will rouse no resentment. Advice and suggestions may be freely tendered. The figure of £20 is given merely by way of illustration. Cheques should be made out to "H. G. Wells Diabetic a/c," King's College Hospital, S.E.5."

Sincerely yours,
H. G. Wells.

This letter raised enough money from some 30 subcribers for my immediate hospital purposes and put into mind the idea of an Association of diabetics for self-help in social matters and to raise money for research, really my main interest. This was the start of our Diabetic Association and the movement was soon inaugurated at our annual hospital dinner where we diabetic subscribers ate our special privileged food and talked over the idea.

Next the sympathy of various doctors specially interested was sought and, with them and the patients they brought, the movement was started, almost entirely in London. I soft-pedaled my interest in starting the movement, an interest which (as a diabetic myself), was really altruistic but might have been, and in some quarters was, considered a Lawrence "stunt".

I shall never forget the first meeting in Wells' apartment of some 50 earnest people, diabetics from all ranges of life. We knew we wanted to do something good and important for the lives of diabetics and the progress of knowledge. But how and where and what, was vaguely tentative in our minds. However, we formed a Diabetic Association on the spot with Wells as President, an advertising expert as Secretary, an accountant As Treasurer, a small Council of lay diabetics with a few doctors, and determined to publish a Journal to unify and spread our efforts, at first in such diabetic clinics as were in being throughout the country.

So it started and spread slowly but surely and our quarterly journal consisted of useful simple advice to patients on diet and insulin. Soon it became incorporated legally in law as a philanthropic non-earning association by which means income tax is avoided and other privileges gained. Fundamentally the organisation and directive power has always been in the hands of lay diabetics and our constitution insists on a preponderance of lay diabetics on the governing council in excess of the interested doctors who also cooperate — only one-third of the total council can be practising physicians earning money from the treatment of diabetics. This has proved a good rule which we have never seen reason to change. The conjoined work of doctors and laymen has always remained happily co-ordinated with no divergent strains and stresses — perhaps a unique situation, though common enough in the practical compromise ingrained in this country when occasional divergent interests meet.

Perhaps an unusual feature in our Association was the different grades of membership we created for the relatively rich and poor. The former became full members with voting rights for an annual subscription of one pound (5 dollars then) and the others paid two shillings (half a dollar) for membership which included their receipt of the same quarterly journal established in 1934.

Such was the beginning — an association essentially for lay diabetics: to help them in their social and personal problems — but not to advise them on their personal treatment which was their own doctors' concern: to educate and encourage them to lead a normal life without handicap from their disease and to dispel invalidism: to fight old-standing prejudices concerning their employment and insurance.

Since the early days, with an ever-growing membership, we have done more and more. Before the war we had holiday homes for children on a small scale and these are now happily recreated for some 300 children. Other fields of activity have been set up with two convalescent homes for men and women. Five educational homes have been established for children from 3 to 16 whose lack of care at home in poor families make their lives and education impossible. We have strained our finances lately — almost to bankruptcy — by setting up a home for elderly poor and uncared-for diabetics. And we endow at present five young and keen research workers on diabetes in different hospital laboratories.

But enough of our present efforts. It was the beginning 20 years ago that I set out to describe. But it is good to feel that the little fire we lit has led to Diabetic Associations all over the civilised world and, indeed, recently to an International Diabetes Federation of all national associations which met this year in Holland.

ASSOCIATION NEWS

POSTGRADUATE COURSE IN DIABETES AND BASIC METABOLIC PROBLEMS

As announced in the last issue of DIABETES, the First Postgraduate Course ever conducted independently by the American Diabetes Association is to be given January 19, 20 and 21, 1953 at Toronto, Canada.

The Association's Committee on Posgraduate Education, chaired by Edward L. Bortz, M.D., is developing the course. The Director of the Course is Charles H. Best, M.D., Director of the Banting and Best Department of Medical Research of the University of Toronto. Ray F. Farquharson, M.D., is Clinical Director and Andrew L. Chute, M.D., Associate Clincal Director. Dr. Farquharson is Professor of Medicine and Dr. Chute is Professor of Pediatrics at the University of Toronto.

The Course is open to members of the Association and the medical profession. A descriptive brochure will be sent to all members and many non-members by midfall, or may be secured, along with additional information, by writing to the National Office of the American Diabetes Association, Inc., 11 West 42nd Street, New York 36, N.Y.

AWARD FOR PAPER ON DIABETES

Another "first" for the A.D.A. is the awarding of a prize for a paper on diabetes to *medical students* and *internes*. It is indicative of the increasing leadership which the Association is taking in the field of diabetes and basic metabolic problems.

The award which will be given annually, $250, has been made possible through the generosity of the St. Louis Diabetes Association.

Members are urged to encourage medical students and internes in their schools and hospitals to submit a paper. Candidates may select any subject related to diabetes. The paper can be a report of original studies, a biographical or historical note, a case report with suitable comment, or a review of the literature.

Manuscripts must be submitted on or before April 1, 1953 to the Editorial offices of DIABETES: The Journal of the American Diabetes Association, 11 West 42nd Street, New York 36, N. Y. The papers will be reviewed by the Editorial Board, which will take into consideration the value of the material and method of presentation, in selecting the best paper.

FELLOWSHIP IN RESEARCH FOR DIABETES

The New York Diabetes Association has just announced the availability of $2,000 for aid in research on diabetes for residents, or prospective residents, of Greater New York.

This amount may be applied for in its entirety or in part, and may be devoted to the purchase of materials or other expenses for entire projects, or for the aid in projects which are being undertaken for which insufficient funds are available.

Applications should be submitted to Theodore L. Kingsley, Executive Officer, New York Diabetes Association, Inc. 2 East 103rd Street, New York 29, N.Y., and should contain the following information: name of applicant, address, past schooling, experience, publications, laboratory or clinic in which work is to be carried out, amount of money required and specific description of the proposed project.

BINDER FOR DIABETES

Arrangements have been made to provide members and subscribers with sturdy and attractive insert binders for DIABETES. The binders will be especially made by a well known company to hold six issues, forming one volume, and are available at $2.00 each.

As a further service to DIABETES readers, arrangements are being made to provide *additional* sets of Volume I in an attractive permanent buckram (library type) binding. The cost will be $9.00 each, which, in effect, means that the binder will be free and the only charge will be for the second set of the six copies (one volume) of the Journal. Individuals and libraries there-

by will be able to have their single copies for ready reference as well as a bound set for permanent reference.

INTERNATIONL MEETING ON MICROBIOLOGY

The Sixth International Congress for Microbiology to be held in Rome, September 6-12, 1953, has just been announced.

The course will be divided into the following sections: General Microbiology (cellular structure, physiology, etc.); Special Microbiology (bacteria, fungi, viruses and rickettsiae, protozoa, transmitting agents, etc.) applied to human, animal and vegetal pathology, and to hygiene, agriculture and industry; Immunology; Classification and nomenclature of micro-organisms. Further information may be secured by writing to: VI Congresso Internazionale di Microbiologia, Instituto d'Igiene "G. Snarelli," Citta Universitaria, Roma (Italia).

PAPERS ON TUBERCULOSIS REQUESTED

The American Trudeau Society, Medical Section of the National Tuberculosis Association, invites the submission of abstracts of scientific papers for presentation at its next annual meeting in Los Angeles, California, May 18 to 22, 1953, at the Hotel Statler.

Full information can be obtained by writing to the Chairman of the Medical Sessions Committee, American Trudeau Society, 1790 Broadway, New York 19, N. Y.

NEW HEART RESEARCH JOURNAL

The American Heart Association has annuonced a new scientific publication, *Circulation Research,* which will be devoted exclusively to fundamental studies related to the heart and circulation.

The journal will be edited by Dr. Carl J. Wiggers, Professor and Director, Department of Physiology, Western Reserve University School of Medicine, Cleveland, Dr. Robert S. Alexander, Associate Professor of Physiology at the same institution, will be Assistant Editor.

Circulation Research will be issued bimonthly beginning January, 1953.

CORRECTION

On page 330 of DIABETES, Volume 1, Number 4, July-August 1952, the price of Dr. Med. Georg R. Constam's book, "Leitfaden fur Zuckerkranke" (in German), published by Benno Schwabe & Co., Basel, Switzerland, 1951, was given as $12.50. This should read 12.50 leinen francs.

"Leitfaden fur Zuckerkranke" is not available at Grune & Stratton, who are the New York representatives of Benno Schwabe & Co., but it may be obtained from Stechert-Hafner, book importers, 31 E. 10th Street, New York City, for $3.40 plus postage.

OBITUARIES

NORMAN CHARLES OCHSENHIRT, M.D., of Pittsburgh Pennsylvania, a member of the American Diabetes Association since October 1946, died at his home in Pittsburgh last August at the age of 60 years.

Dr. Ochsenhirt was a native of Pittsburgh and obtained his medical degree from the University of Pittsburgh in 1917. After three years at the Mayo Clinic, he received his M. S. in Surgery in 1927 from the University of Minnesota. He served in the Medical Corps of the United States Army from July 1917 to August 1918. He was a surgeon at Suburban General Hospital, at Montefiore Hospital, and Presbyterian Hospital Medical Center, University of Pittsburgh.

His teaching duties included professorships in maxillofacial surgery and general pathology at the Dental School of the University of Pittsburgh. He was a member of the Allegheny County Medical Society, the Pennsylvania State Medical Society, The American Medical Association and The Pittsburgh Surgical Society and was a fellow of both the American College of Surgeons and the International College of Surgeons.

LEO KEMPF CAMPBELL, M.D., Ph.D., of Chicago, who was a member of the American Diabetes Association from 1945 to 1951, died at Presbyterian Hospital, Chicago, on June 13, 1952, of heart disease at the age of 52.

Doctor Campbell received his Ph.D. in Pathology at the University of Chicago where he studied under the pathologist, H. G. Wells. He then completed his medical training at Rush Medical College in 1927, serving an internship at Presbyterian Hospital, and becoming associated in practice with Dr. Rollin T. Woodyatt.

He conducted research in diabetes at the Sprague Institute of Rush Medical College and Presbyterian Medical Hospital and conducted the practice of internal medicine up to the time of his terminal illness last year.

Doctor Campbell was a clinical professor of medicine at Rush Medical College and later at the University of Illinois College of Medicine. He was affiliated with the Presbyterian Hospital and for a short time was one of the directors of the Chicago Diabetes Association. A native of Frankfort, Indiana, Doctor Campbell is survived by his widow, his mother, a sister and two brothers; one, Dr. Paul Campbell, also of Chicago.

FOR THE DIABETIC

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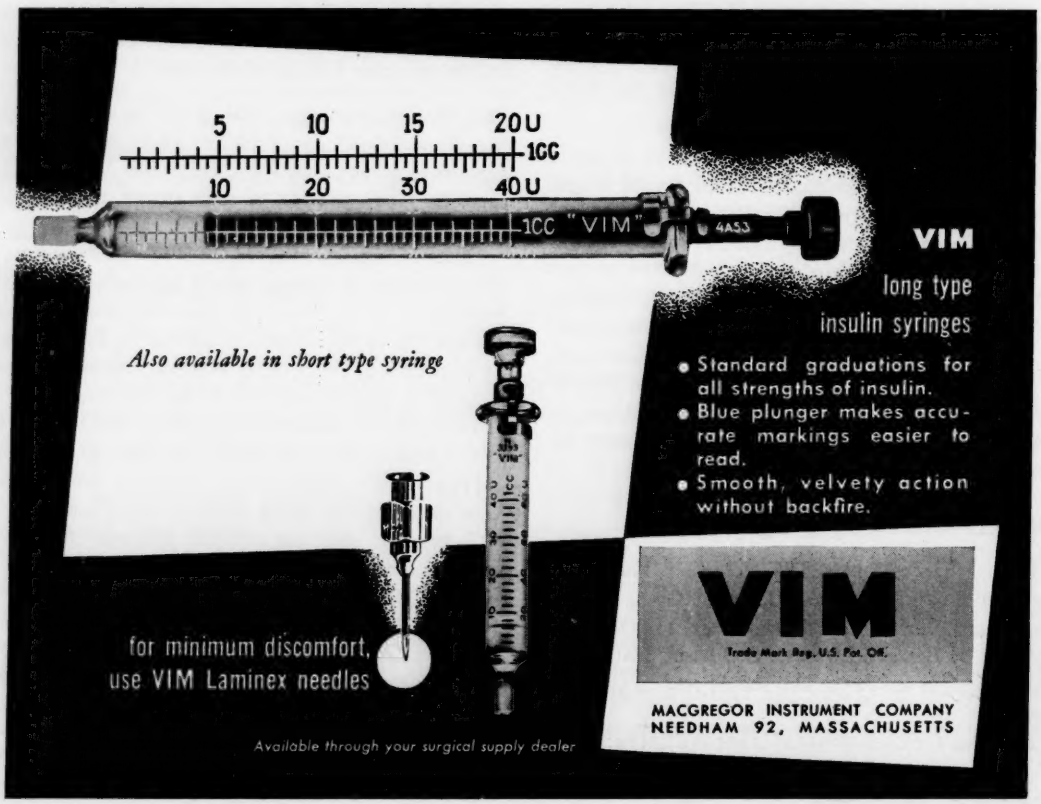
Subscription rates: 1 year, $2.00; 2 years, $3.50; 3 years, $4.75. Add 25c per year for subscriptions outside the U.S. and Canada.

Subscription Department, A.D.A. FORECAST
American Diabetes Association, Inc.,
11 West 42nd Street, New York 36, N. Y.



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